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THE TREATMENT OF SEPSIS IN SCARLATINA WITH ANTISTREPTOCOCCUS SERUM

MATTHIAS NICOLL, M.D.
NEW YORK

In using the term sepsis in scarlet fever I desire to be understood as referring to a set of clinical symptoms occurring forty-eight hours or longer after the onset of the disease, which are apparently due to the invasion of the body by organisms of the streptococcus group, which, up to the present time, are not known to possess any cultural or other characteristics which serve to distinguish them from streptococci isolated from a number of other morbid conditions. The symptoms may be briefly stated as follows: No fall of temperature, or a renewed rise; abnormal swelling of the mucous membrane of the throat, with or without superficial sloughing; profuse nasal discharge; marked cervical adenitis; rapid, often irregular pulse; mental apathy; active or low delirium. Streptococci may or may not be found in the blood, and it should be said that while they are usually present in prolonged cases especially, they are not necessarily so, even in those which must be clinically regarded as septic and, on the other hand, may be found at an early stage in cases whose course is otherwise benign and which do not admit of other than a technical diagnosis of this condition.

Until the organism which causes scarlet fever has been definitely determined we must continue to regard those cases which are overwhelmed by the onset of the disease and are likely to succumb in twenty-four to forty-eight hours as directly due to this undetermined cause. Such are, in this country at least, of comparatively infrequent occurrence. The greater number of severe and fatal cases being of the class the symptoms of which I have described.

Scientific workers on the problem of scarlet fever seem more and more inclined to disregard the possibility, formerly so generally advocated, of streptococci representing anything more than the invasion of a secondary organism on a soil suitably prepared by some unknown agent. If this view proves to be correct, it must be confessed that certain well-authenticated phenomena are thus rendered most difficult of explanation. Of these I may mention the undoubted success of vaccination with killed streptococci from scarlet fever patients as a means of preventing the latter. This work has been largely confined to Russia and apparently

has caused but little interest in this country. Of the recent reports I may mention that of Tesjakoff, who in a study of 15,000 vaccinated patients, reaches the conclusion that three inoculations extending over two weeks is able to protect against the disease. Again Raíkowa, making observations in seven epidemics, on 721 vaccinated patients, found that among 524 patients vaccinated but once nine cases of scarlet fever occurred; among 122, vaccinated twice, five cases, while seventy-five patients vaccinated three times remained free from the disease.

Verhoff points out that the death-rate in 403 vaccinated patients in whom scarlet fever occurred was but 6 per cent., compared with a rate of 17.5 per cent. in the unvaccinated. Furthermore, all those who have made use of vaccination, from Gabritchewsky, who originated it, to the present, agree as to the common occurrence in those inoculated, of symptoms which cannot be distinguished from those of scarlet fever of the milder type as regards the onset, course, rash and occasional complications. Again, if the streptococcus be eliminated, how are we to account for the good results of the antiserum in Moser's fourth category of cases —those patients overwhelmed by the first rush of the disease—which showed a mortality of 100 per cent. without serum, and 65 per cent. or less with its use?

Two recent attempts to do away with the streptococcus as a causative factor are of interest. Cantecuzène, of Bucharest, reported to the Société de Biologie in April, 1911, that he had inoculated nine of the lower monkeys with bronchial glands, pericardial exudate and blood, the latter two free from streptococcus, taken from scarlet fever patients, and produced what appeared to be in all respects true scarlet fever, having an incubation period of seven to thirty-five days, and followed by typical desquamation. I am authorized by Dr. William H. Park to state that six monkeys (*Macacus rhesus*) injected with the blood of six different scarlet fever patients not tested for streptococcus, failed to show any symptoms of the disease, one dying after a few days of ileocolitis. Dr. George Bernhardt of Berlin, working under Gaffky, reported in April that by inoculating a number of lower monkeys with suspensions of tongue-scrapings, serum and enlarged nodes of scarlet fever patients, subsequently excising the enlarged inguinal nodes near the site of injection, grinding and passing the latter through other monkeys, he was finally able to procure nodes showing no streptococcus or other organism, whose further inoculation into another series of monkeys caused symptoms in all respects similar to those in scarlet fever of human beings.

If this work can be confirmed, it must be conceded that the streptococcus can no longer be regarded as the causative factor or essential to its development. Until this is accomplished it would seem wise to have an open mind on the subject, especially as it is becoming daily more evident that with greater refinement of technic and newer methods of differentiation, we may soon be able to assign to the various strains of

these organisms specific characteristics in the production of different morbid conditions, one of which may be scarlet fever.

The serum treatment of scarlet fever, first brought into prominence by Moser, whose name is usually associated with a serum produced by the inoculation into horses of streptococci taken from many patients with scarlet fever, was, like most specific remedies, hailed at first with the greatest enthusiasm, and, like most specifics, the results obtained did not fulfil popular expectations. If one consults the now fairly voluminous literature on the subject, he is sorely puzzled to account for the contradictory opinions set forth as to the worth of the serum. This, in part, is to be explained, I believe, by difference in the methods of its employment, whether used early, or only late, in moribund cases; differences in the type of the disease, not only locally, but as between different countries; and finally, by judgment founded on too few cases. There is, furthermore, undoubted difference in the antitoxic strength of sera and not unnaturally a prejudice against the use of the huge doses which seem essential to the production of results.

I shall refer to but one set of observations, those of Fedinski of Moscow, published in 1910, who in a most elaborate analysis of 317 cases in which serum was used, compared with about 900 cases without it, comes, as it seems to me, to the very reasonable conclusion that the serum given in full doses before the fifth day greatly increases the chance of recovery, even in the apparently hopeless cases; that in a large majority the temperature falls by crisis within twenty-four hours, or, if by lysis, the course of the fever is shortened. The occurrence of complications is less frequent and their gravity diminished. The influence on the heart's action, central nervous system, the rash and on necrotic processes is marked. The dosage in the average severe case was 200 c.c. subcutaneously, except in the case of young children, when 100 to 150 c.c. were given, and this dose was repeated in from twenty-four to forty-eight hours if necessary. Chart 1 shows the deaths from scarlet fever in the City of Moscow for a series of years. The solid line represents those patients who died outside the hospital, the dotted line those receiving hospital treatment. It will be noted that the average of the hospital deaths held well above those dying in the city, but that with the beginning of serum treatment in the hospitals, and especially in the second year of its use when others than the apparently hopeless patients were thus treated, the hospital patients show a death-rate well below those treated outside and without serum.

In this country the serum treatment of scarlet fever has, as far as I know, been but little tried. My own experience was obtained at the Scarlet Fever Hospital of the Department of Health of New York City during February, March and April, 1910, in the course of a very extensive epidemic of the disease. The serum used was that prepared under the direction of Dr. Park, consisting of eleven strains of streptococci from scarlet fever patients—blood, throat, glands, etc., and one of strepto-

coccus from a case of endocarditis. Owing to a somewhat limited supply at the time, it was thought advisable to give but 50 c.c. as an initial dose, which of course precludes the possibility of comparison with the European results. In so far as was possible in a badly overcrowded hospital, with overworked staff and nurses, every patient who showed markedly grave symptoms, regardless of the day of disease, was injected by the staff or myself and visited by me daily, with the exception of four cases furnished me by the resident physician. By no means all the fatal cases during these months were the patients injected, as measles, diph-

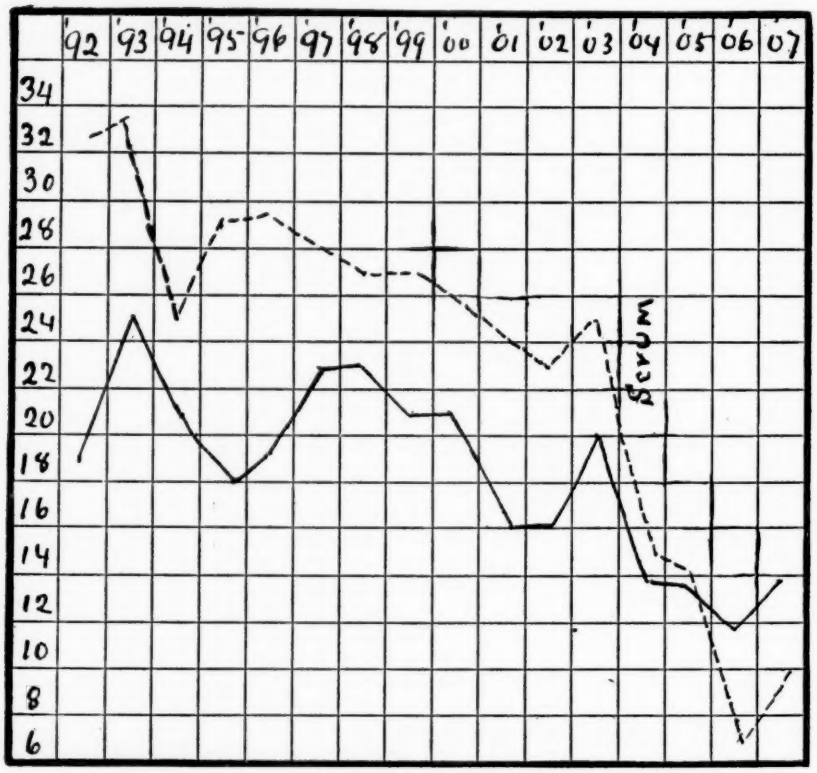

Chart 1.—The solid line shows the mortality curve from scarlet fever in Moscow from 1892 to 1897; the figures on the left show the percentage; the dotted line shows the mortality in the Vladimir-Kinderhospital during the same period under serum treatment.

theria and other complications accounted for their unfavorable progress and often death. Again, patients who, in spite of the severity of onset, seemed to be in no immediate danger, not infrequently took so sudden a turn for the worse that there was no opportunity to make use of the serum.

There were injected in all, thirty patients, of whom seventeen died; not a very brilliant showing, it must be confessed, but on analyzing the

fatalities, the poor results may be reasonably accounted for without detracting from the value of the serum. Of these seventeen cases, four patients were brought in the hospital in a moribund condition, immediately injected, and died within a few hours. Of those who were ward patients twenty-four hours or longer, one died within two hours after receiving injection, two others within twelve hours, a length of time too short to hope for any relief from a subcutaneous injection. Another patient, after seeming to respond favorably, contracted measles and ileocolitis; another measles, followed by gangrenous varicella. The condition of three others was shown to be due to a complicating diphtheria which failed to yield to large doses of antitoxin following the serum. One patient was injected late in the disease, with the hope of affecting a double mastoiditis, 100 c.c. being given intravenously. The result was inconclusive, as an operation was thought desirable. Following this, the patient received 100 c.c. subcutaneously, grew gradually weaker, with no marked lowering of the temperature, which had been exceedingly high, and died two weeks later in extreme emaciation. This leaves four patients in whom the failure of the serum must be accounted for on other grounds than those just described.

CASE 1.—H. H., aged 7, had been ill three days on admission; temperature 104.2 F., pulse 144, respiration 32; glands in the neck greatly swollen; patient looked extremely septic. The patient was given 100 c.c. of serum subcutaneously, pulse, respiration and temperature falling the next day and the temperature not going much above normal until just before death. Ten days after receiving treatment, the heart action became very unsatisfactory; the patient looked very pale and weak; stimulation seemed to have no effect, the pulse growing weaker and more irregular day by day. A few days later, the patient developed general choreic movements, followed by arthritis of the left wrist, and died three weeks after admission apparently of heart failure due to myocardial involvement.

I have the records of two cases similar to this in patients who were given 150 c.c. intravenously for a very grave mixed infection with diphtheria. The local throat symptoms cleared up readily under the combined use of antitoxin and serum, but the patients both died a week or more later, one with a very rapid heart action, and the other with a pulse which fell from 120 to 53.

CASE 2.—S. McB., aged 4, ill eight days; throat very much swollen; cervical nodes greatly enlarged; patient profoundly septic and delirious; temperature 104, pulse 180. The patient was given 50 c.c. of serum and died thirty-six hours later without any apparent amelioration of conditions. The failure of the serum in this case may be reasonably attributed to the length of time the patient was ill.

Following are two cases (3 and 4) in patients of Dr. Sexton, the resident physician, whom I did not see. They were, however, very carefully studied and the pulse and temperature taken every two hours, before and after the administration of serum.

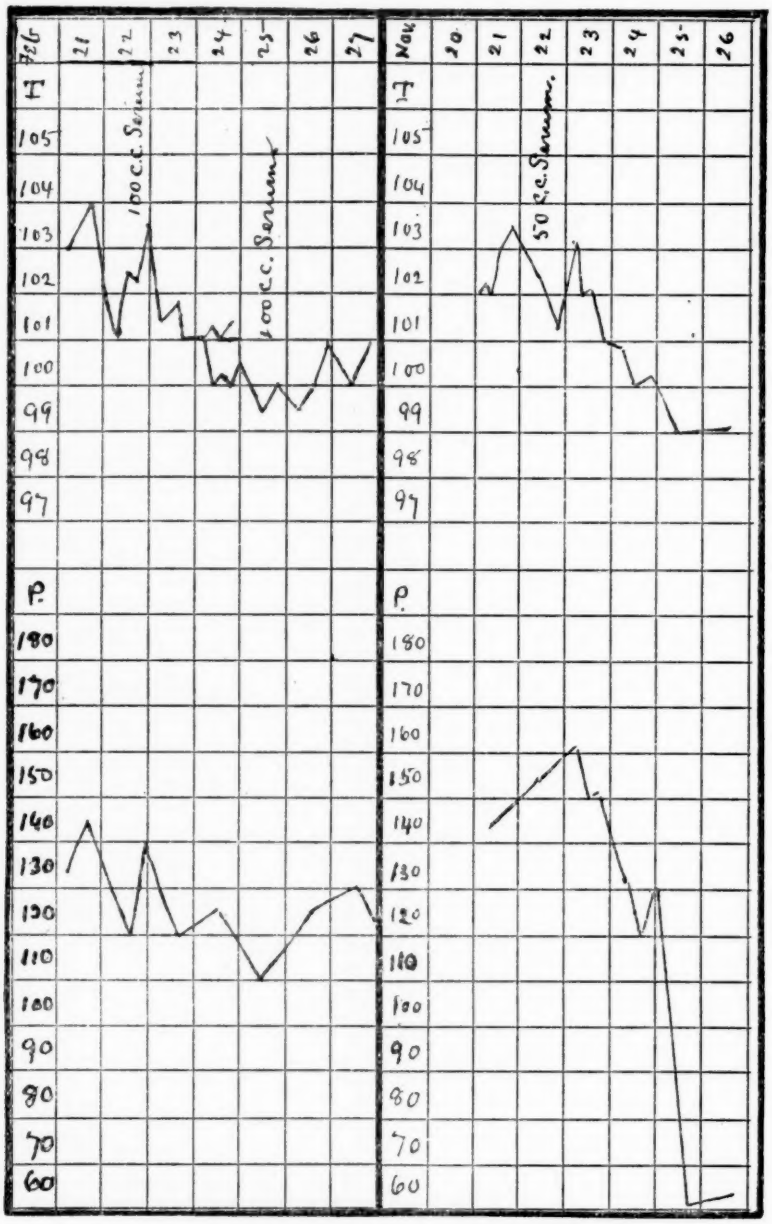

Chart 2. Chart 3.

Chart 2.—Shows the effect on temperature and pulse of serum administered in Case 5.

Chart 3.—Showing effect of serum treatment in Case 6.

CASE 3.—J. K., aged 2, had been ill four days on admission November 17, when the temperature was 103.4 F., pulse 140, respiration 32. This condition did not change markedly during the next five days. The cervical nodes were very much swollen; the pulse at times was imperceptible. On the ninth day of her illness she was given 50 c.c. of serum and died thirty-six hours later without any appreciable effect having been produced.

CASE 4.—J. M., aged 16, was admitted November 14. November 23 the temperature was 104.5 F., pulse not countable, respirations much increased. The next day when the 50 c.c. of serum was given the temperature was 101.2 F., pulse 180, respiration 144. The patient was markedly septic, cyanosed, and wildly delirious, heart sounds muffled, pulse hardly perceptible. Temperature the next day was 100 F., pulse 160 and of a better quality; respiration 36. On the second day his temperature dropped to 97 F., pulse to 104 and respiration to 36. The patient was still cyanosed and very delirious. Mouth and nose discharged profuse bloody secretions. The third day the patient was still delirious, though the pulse was of better quality. On November 28, four days after giving the serum, the temperature was 100 F., pulse 152, respiration 36. The color was better and the pulse of a fair quality. Nourishment was taken well; nose and mouth were still bleeding. Later in the day, the condition became suddenly worse; the patient became cyanotic and died of heart failure.

If the serum had been given in anything like sufficient quantities at an earlier stage in these two cases, it is possible that it might have been successful in its action.

Of the patients who recovered, a short history of a few will serve to show the apparently good effect of the serum.

CASE 5.—S. K. (Chart 2), aged 10; ill two days on admission; covered with an intense dusky rash with much vesiculation; throat and cervical lymph-nodes very much swollen; lips dry and fissured; constant muttering delirium; 100 c.c. of serum given subcutaneously. The next day the temperature fell; the delirium continued. The following day, 100 c.c. serum was given. There was a general and profuse desquamation over the whole body; the patient was not delirious, but very stupid. The day following there was a marked improvement in the general condition. The subsequent history was one of convalescence, interrupted by multiple arthritis in the third week. The patient was discharged in good condition after a long stay in the hospital.

CASE 6.—E. R., aged 7 (Case of Dr. Sexton). The patient had been ill six days on admission, was profoundly septic, gums and lips sloughing, teeth dropping out, eyes injected and excreting profusely, cervical nodes much swollen, patient unconscious. He was given 50 c.c. of antistreptococcus serum on the second day after admission to the hospital, when his temperature was 102.3 F., pulse 150, respiration 132. The subsequent course of his temperature and pulse is shown in chart 3.

Two days after receiving serum, the condition of the mouth and gums had very much improved. On the sixth it was noted that the patient was crying for food. On the eighth the pulse, temperature and respiration were normal and the recovery was complete.

CASE 7.—L. J. (Chart 4), aged 15, had been ill two days on admission; very toxic; vomiting was constant; throat was very much swollen, also the cervical nodes; pulse very rapid and feeble. Improvement took place in twenty-four hours, with uneventful recovery, after the administration of 100 c.c. of serum, given on the third day after her admission to the hospital.

CASE 8.—R. S. (Chart 5), aged 6½, ill two days. Dr. Sexton, who observed the case throughout, noted that the patient was wildly delirious, but did not regard her as septic. The temperature was 105.5 F., pulse imperceptible, respira-

tion 44. She was given 50 c.c. of serum on her admission to the hospital; twenty-four hours later the delirium was less marked and the temperature and pulse were down. The following day the patient's condition was excellent, delirium had ceased, and recovery was very rapid.

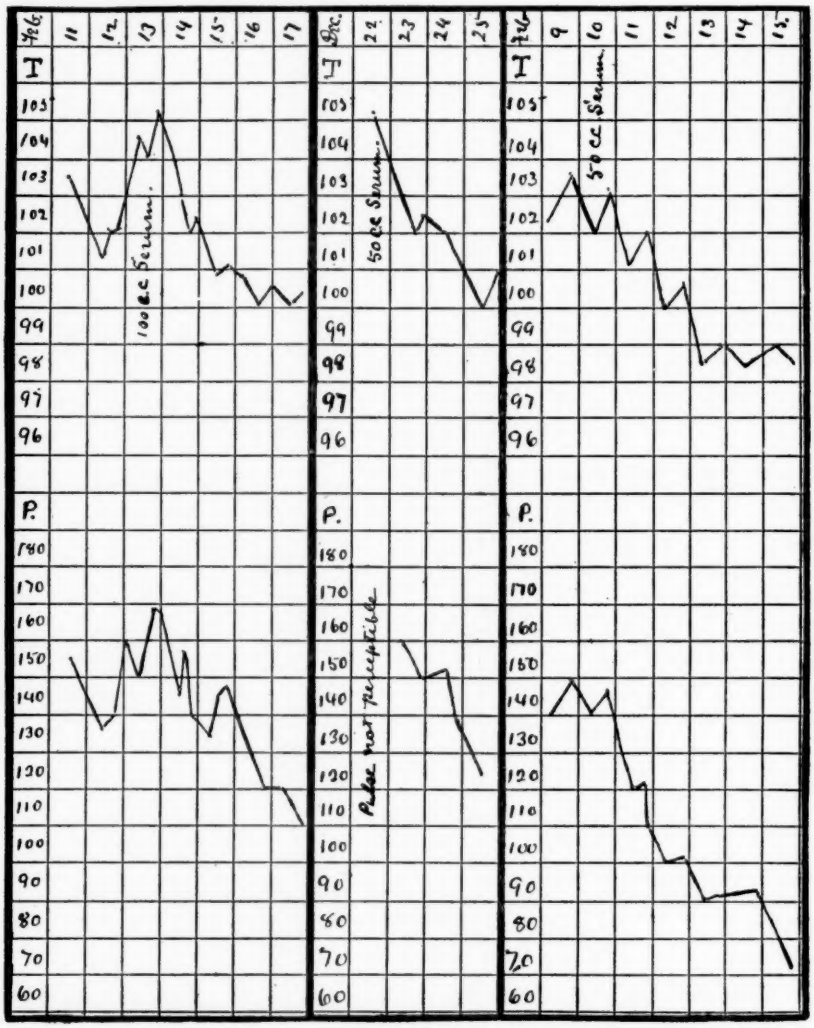

Chart 4. Chart 5. Chart 6.

Chart 4.—Effect of serum treatment in Case 7.

Chart 5.—Result of serum treatment in Case 8. Patient ill only three days.

Chart 6.—Showing drop in pulse and temperature after administration of serum in Case 9.

CASE 9.—H. S. (Chart 6), aged 10, had been ill two days on admission. The patient was very septic, with swollen throat and cervical nodes. Fifty c.c. of serum was given on the fourth day of her illness. Temperature and pulse fell by rapid lysis, and recovery was uneventful.

These examples are sufficient to illustrate the apparent effect of the serum on the pulse and temperature, and on the general and local septic conditions.

In a number of other cases in which the temperature was not so high, but in nearly all of which the pulse was very rapid, the effect of the serum was marked. The following illustrates its usefulness in local conditions about the nose and throat.

CASE 10.—S. K., aged 8½, had been ill five days on admission. The patient was apparently suffering from marked general sepsis, with profuse, foul, dark-colored nasal and oral discharge, with great swelling of the cervical nodes; lips also markedly swollen and fissured. The patient's mouth was wide open all the time. He was extremely apathetic. On the eighth day of his illness he was given 50 c.c. of serum, at which time the temperature was 101, the pulse 140. The amount of discharge from his nose and mouth was simply appalling. The temperature the next day rose 2 degrees; the pulse fell slightly. The following day the pulse fell to 110, the discharge showed very marked improvement and a few days later had ceased, the patient making an uneventful recovery.

What bad effects from the serum may be expected? In the foreign statistics rashes of various kinds occurred in a large number of cases, generally, however, of an urticarial type; also rise of temperature, evidently due to the same cause in about half the number, and occasionally polyadenitis, arthralgias and localized edemas. In my experience, I should say that with a dosage given subcutaneously, even of 50 c.c., an urticarial rash was the rule rather than the exception. Other and severer forms of rash I have not seen. A moderate rise of temperature accompanying the rash is not infrequent. Polyadenitis and arthralgias which could be definitely attributed to the serum were not noted. One case of true anaphylaxis occurred recently:

CASE 11.—P. P., aged 5, was admitted January 28, after one day's illness with scarlet fever and diphtheria. He was given 6,000 units of antitoxin on admission, and on the following day, as his throat seemed worse, 10,000 units. The patient had a tuberculous hip joint and was in generally poor condition. His subsequent history was that of chronic sepsis, with double mastoid infection, requiring operation, and abscesses in various parts of the body which when opened healed very badly.

April 17, seventy-nine days after admission to the hospital, a blood-culture was made and immediately antistreptococcus serum was allowed to run into the same vein. It ran very slowly, not more than 10 or 15 c.c. entering the vein, when the patient, who had been whimpering, gave one or two sharp coughs and attempted to vomit. The face became intensely cyanosed, and then deathly pale, except for a purple band extending across the forehead and eyes. The needle was immediately withdrawn, and the patient put to bed. He was unconscious, his color absolutely death-like; the pulse could not be felt; a dusky erythema covered the whole front of the body. The respirations, which had previously been 38 to 40, varied from 15 to 22 a minute with deep inspiration, very noisy and drawn through closed teeth. A few minutes later a purpuric rash covered the right limb from hip to ankle, the color disappearing only under long pressure. On the inside of the left leg, was a rash somewhat scarlatiniform in character.

These rashes disappeared in half an hour, except on the inner side of the right foot, where a circinate rash took the place of the purpuric. Under active stimula-

tion and heat, consciousness returned within an hour and the patient recognized those about him. There were râles at the bases of both lungs which had not been noted previously. The next day the pulse, temperature and respirations were about as they were previous to the injection. On the following day there was an exanthematous rash on the scalp, and a patch of erythema in front of the right ear. The subsequent history of the patient was one of progressive emaciation, death taking place about ten days later.

Whether these phenomena would have resulted from a subcutaneous injection I am unable to say. In another case, not scarlet fever, the patient developed a severe local anaphylaxis followed by an extensive area of sloughing at the point of inoculation following her eighteenth subcutaneous injection, the previous injections having caused nothing more than a mild urticaria. For this apparent lack of immunity to horse-serum, after seventeen injections given at short intervals, I have no explanation to offer, unless it is to be regarded as an example of the Arthus phenomenon. I have had an opportunity during the last few months to observe the effect of large doses of this serum given intravenously, and with the exception of the case mentioned I have not seen any alarming results which could be attributed to this method of administration. However, I am not prepared at this time to recommend its general use in this way, except in those cases in which a delay of twelve hours would probably determine a fatal outcome. Here, intravenous injections are by all means to be preferred.

Until there is some method of standardization and concentration of the serum, it would seem highly desirable to use a dosage believed to be essential to the best results by those who have had most experience with it, namely, for older children and adults, 200 c.c. injected, by preference, one-half into each side of the lower abdomen; for infants and young children, 100 to 150 c.c. in all.

The apparatus employed has been used for a number of years in the New York Department of Health for the inoculation of horses with large doses of serum, and I have found it most convenient for clinical purposes. It consists of a glass container, which may hold from 100 to 200 c.c., a rubber tube sufficiently long to be convenient, and a force pump which serves to give enough pressure to cause the serum to enter the tissues through the needle. It may be used equally well for intravenous injection. Care should be taken to see that the serum is heated to 100 F., otherwise a chill will result.

Finally, while my somewhat limited experience with this remedy does not entitle me to form a decided opinion, I cannot help but feel that in a disease over which we have little or no control, and which so frequently goes unexpectedly wrong, in all severe cases of scarlet fever, the serum, if attainable, should be made use of in full doses and without delay.

124 East Sixtieth Street.

ACCESSORY SINUS SUPPURATION IN SCARLATINA*

THOMAS HUBBARD, M.D.
TOLEDO, OHIO

As would be naturally inferred from the title, this article deals almost exclusively with the acute scarlatinal sinus suppuration of childhood. If the rhinologist of to-day is to do his whole duty he must be alive to the fact that the exanthematous diseases of childhood, and particularly scarlet fever, often present certain complications in the line of acute sinus infections that are quite as important, as concerns the immediate and future welfare of the child, as the well-understood acute ear infections.

Grünwald[1] contributes the valuable experience of a careful observer in tracing cases of chronic suppuration back to the primary cause. He includes pneumonia, typhoid fever, diphtheria, and particularly scarlet fever, as causes of the initial infections. Most of the authorities in pediatrics mention sinus suppuration (maxillary chiefly) as a complication of scarlet fever, but none of them emphasizes its importance in a manner sufficient to stimulate a proper conception of this disease process, and certainly not in the manner to put this complication in its proper place as a definite disease condition that should be studied and treated from the standpoint of a rhinologist.

We have now a better understanding of the factors that contribute to the virulency of secondary nasal diphtheria as observed in pre-antitoxin days, knowing that even in young children there are vulnerable accessory sinuses which, once invaded, add to the specific toxemia a septic condition which makes these cases so invariably fatal. I have seen this condition in scarlatina: pansinusitis, pus discharge, localized edema over frontal and orbital regions, as the chief objective symptoms progress to a rapidly fatal issue and did not label it properly as the first step toward rational treatment. Between this severe type and the so-called purulent rhinitis type, frequently seen in connection with the exanthemata, and which usually recover, but with perhaps a chronic suppuration or catarrhal condition, there is a group of cases which have well-developed sinus suppuration. These deserve careful study and special local treatment, and failing in that they may be amenable to more or less radical surgical treatment.

To begin with, we should treat the acute rhinitis of scarlet fever as a definite infection of the nasal mucosa, liable at any time to invade the

*Read at the meeting of the American Laryngological, Rhinological and Otological Society, Atlantic City, June, 1911.

1. Grünwald: Nasal Suppuration, 1900, 2 Ed., Wm. Wood & Co., New York.

sinuses and not, as the present practice prevails, chiefly with the object of preventing ear infection. Keeping this precept clearly in mind the alert rhinologist will not be surprised with a well-developed purulent sinusitis on his hands. Not that he can always prevent it, but he will not be led into taking part in a vain hunt over the whole anatomy for the cause of post-scarlatinal fever and retarded convalescence, and finally be pushed into the embarassing position of making the sinus diagnosis by exclusion. That is to say, if nothing else, it must be a suppurating sinus.

Suppurative rhinitis *per se* is a rare condition—at least to the degree that one is quite justified in assuming that pus from the nares means purulent sinusitis. The fact that spontaneous cure occurs does not prove that the sinuses were not involved.

We are in the habit of regarding the sinuses as being anatomically unimportant in childhood. They are only in process of development from 5 to 12 years of age, the ostia are proportionately large and if infected are relatively less liable to empyema than in adults. But scarlet fever breaks many pathologic ordinances, and we certainly must learn to recognize sinus suppuration in children even though the anatomist teaches that it is improbable. The maxillary sinus and the ethmoid cells are the most constant in early childhood, but even prior to 10 years of age the frontal and sphenoidal sinuses are sufficiently large to be invaded.

Another factor in leading the rhinologist off the scent, as it were, is that he is likewise an otologist. The ear trouble is usually more in evidence at this stage and he is distracted by the danger thereby entailed and, perhaps, is attracted by the urgent surgical indications. He opens the mastoid, exenterates the process and hopes that his surgical duties are over. Usually they are, but not always. An infectious process that can penetrate to the middle ear would naturally be expected to invade cells and sinuses that are directly accessory to the mucous tract primarily invaded. All otologists can recall cases of this character in which the healing of the mastoids was very slow, and in spite of perfect ear surgery the discharge continues through the tympanic membrane, gradually destroying all chances of restoration of hearing. Unaccountable fever persists and convalescence is retarded. Sometimes this is attributable to adenoids or extensive lymphadenitis, but occasionally it is sinus suppuration. Remember that in children pus is not always in evidence unless there is ethmoid edema to the degree of blocking the flow into the throat. It must be searched for, and even then it is more difficult to trace to its source than in the adult.

In a classical article by Killian,[2] the pathology and surgical indications are clearly presented. Killian records six cases coming under his

2. Killian: Die Erkrankungen der Nebenhölen der Nase bei Scharlach, Ztschr. f. Ohrenh. u. Krankh. d. Luftwege, September, 1908.

observation and surgical treatment, in all of which the patients suffered from sinus suppuration due directly to scarlatina. Three of these were acute, and as it is this class in which we are particularly interested, a brief review of them will be given.

KILLIAN'S CASES

CASE 1.—Boy, aged 11. On the eighth day of scarlatina severe frontal headache, local tenderness and swelling of the left orbital tissues were noted. The nasal discharge contained streptococci. Systemic symptoms indicated lung involvement and also nephritis. Local symptoms of sinus suppuration increased, with edema and tenderness over the frontal and maxillary sinus areas. Metastatic abscesses followed and the child died on the fifteenth day. The autopsy showed septic thrombosis of the superior longitudinal sinus consequent on general accessory sinus empyema, leptomeningitis and metastatic abscesses in the lungs.

CASE 2.—Boy, aged 6. On the twelfth day of scarlatina tenderness and edema over the left frontal sinus and orbital edema, together with general sepsis and local pus discharge, enabled Killian to establish the diagnosis of acute frontal sinus suppuration. Later maxillary involvement was in evidence. Although the general symptoms indicated possible sinus thrombosis—superior longitudinal or cavernous—yet operation was decided on and performed by Killian on the thirteenth day of sickness. The ethmoid and sphenoid cells were explored through the orbital opening and found to contain pus and granulations. The frontal sinus, although very small, and the maxillary sinus were full of pus. Drainage was established into the nose by the removal of the anterior third of the middle turbinate and the maxillary antrum was irrigated for about two weeks through the canine fossa opening. Streptococcus serum was administered. Recovery was rather slow but complete.

CASE 3.—Girl, aged 12. Operation was made in 1905 by Killian, by the intranasal method, about the forty-fifth day of scarlet fever. The principle symptoms were, pus from nares, from frontal, ethmoidal and maxillary sinuses and marked orbital edema. The diagnosis of empyema was confirmed by radiograph. The maxillary and frontal sinuses were irrigated and ethmoid cells freely opened. Two weeks later symptoms improved but the report closes with expression of doubt as to purulent discharge from the nose.

Three other cases are recorded by Killian in which suppurations of rather more chronic type, due to scarlet fever, were cured by operations by the radical method. Nineteen additional cases recorded in literature are detailed, fifteen of which were in children, the youngest being 2½ years. Of these nineteen cases, fifteen patients were operated on by the more or less complete radical method; that is, through the orbital incision. In nearly all the ethmoid cells, as well as the frontal, were cleaned out and drained, and such as had maxillary involvement were operated through the canine fossa. A few had prior or subsequent mastoid suppuration, likewise operated on. Thirteen of the fifteen patients operated on recovered; that is, only two in whom thorough operation was undertaken. died.

Detailed autopsy reports of nine cases collected from the literature are recorded by Killian. In all of these there was empyema of the accessory sinuses following scarlet fever, but in many death was not directly attributable to this complication. The important point is that accessory

sinus infection is often insidious and in the presence of other grave complications the symptoms are often overlooked. Wertheim finds accessory sinus empyema in one of five autopsies of children dead of scarlet fever, and Moritz Wolf records five findings of empyema in five autopsies of children dead of scarlet fever, three of which had the scarlet fever and diphtheria type. Nineteen diphtheria autopsies by Wolf showed pus in the accessory sinuses, even though many of these patients had exhibited very slight clinical symptoms.

The complications and sequelæ of scarlet fever are so varied and grave that statistics are not of much value unless careful detailed comparisons are recorded, and of course that is impractical and unnecessary in a review of this character. The percentage of recoveries implied by Killian's statistics by no means tells the whole truth as to the mortality of accessory sinus suppuration in scarlatina. Probably many fatal cases are not diagnosed as having sinus disease, and some present no favorable opportunity warranting operation. No doubt some of the fatal operated cases are not reported. But we certainly are warranted in the conclusion that the operation is justifiable, in fact strongly indicated, in many cases presenting a very extensive and serious degree of sinus suppuration and we should include those with symptoms of venous sinus thrombosis, and that, too, with a fair chance of successful termination, even in the hazardous post-scarlatinal condition.

Killian's conclusions are very important: sinusitis is nearly always present in varying degree in the severe rhinitis of scarlatina. Sinus empyema is present in nearly all fatal cases presenting symptoms of purulent rhinitis. However, in some serious cases the discharge may be very slight. Marked intranasal edema over the ethmoid region is always present if the ethmoids are involved. The maxillary antrum is most frequently infected, and as a rule the most advanced pathologic changes are here found, but fortunately there is less danger of serious results from extension than obtains with the other sinuses.

The ethmoidal, frontal and sphenoidal sinuses are alike vulnerable to infection in proportion to their development. The ethmoidal cells are the most constant anatomically in childhood, which accounts for intranasal edema as a prominent symptom.

When we take into consideration the treacherous character of this serious disease we may expect irregular and rapid progress of the disease process. In other words the systemic forces of resistance may be overwhelmed and invasion and destruction may involve the body walls, and produce necrosis such as is often observed in scarlatinal suppuration of the middle ear and mastoid.

The essential objective symptoms of scarlatinal sinus suppuration are: discharge of pus from the naris containing pyogenic cocci, rise of temperature, local edema and tenderness of special sinus areas. Ocular symp-

toms are not very dependable in childhood and exophthalmos is rare. Fatal septic phlebitis or meningitis may follow sinus infection before the local symptoms have developed to such a degree as to attract attention. It must always be taken into consideration that the majority of acute infections of the sinuses subside spontaneously, but this is perhaps less true of scarlatinal sinusitis than of the ordinary type. It is doubtful if any case presenting the symptom-complex in marked degree can recover without spontaneous or artificial complete evacuation of the pus. The tendency toward bone necrosis is characteristic of scarlatinal sinusitis. The most vulnerable points are: in ethmoidal suppuration, the lamina papyracea (os planum); in the frontal sinus, the inner orbital region just above the lachrymal bone, and in the maxillary sinus, the superior wall.

Meningeal invasion is less likely to follow ethmoidal than frontal sinus empyema, probably because of the anatomic fact that there is less resistance intranasally in the former. Anatomically one can see little reason why there should not be quite as frequent dural as periosteal evidences that the inflammation has penetrated through the bony wall. Of course this observation does not apply to the muco-periosteal lining of the sinuses, since that is the seat of primary infection, but certain it is that facial edema over special areas in this serious type of acute infection should be considered a warning that the infection may be likewise progressing through the inner table. A sudden subsidence of periosteal edema may be coincident with meningeal invasion. This undoubtedly occurs in the most virulent type, and intracranial symptoms may supervene and with symptoms which so overshadow the accessory sinus symptoms that they are scarcely considered a factor in the pathologic complex of scarlatinal septicemia.

The bacteriology of scarlatinal sinus suppuration will be dismissed with a few words, as it is in a rather chaotic state and there is nothing definitely known except that pyogenic cocci are invariably found.

The age of the patients makes the ordinary intranasal operations impractical, and conditions are usually so grave that the importance of thorough radical work is essential. There is no question that the radical method—the Killian operation—modified and adapted to the acute condition, is the one to be chosen. Frontal, ethmoidal and sphenoidal sinuses should be explored, granulations and carious tissue removed, and permanent free drainage established. As a general rule a portion of the middle turbinate must be sacrificed to secure perfect ethmoid drainage, and the fronto-nasal duct should be enlarged. As previously stated, the operation must be so thorough and the drainage must be so free that after-treatment will be easy, for a sick child should not be subjected to the daily terror of painful irrigations and dressings.

REPORT OF AUTHOR'S CASE

CASE 4.—*Suppurative Sinusitis Involving Frontal, Ethmoidal, and Maxillary Sinuses, Following Scarlatina, Complicated by Suppurative Mastoiditis. Operation. Recovery.*

History.—Dec. 23, 1910, G. M. J., aged 12, developed acute tonsillitis with otitis media. The primary symptoms were very severe, with false membrane deposit on the tonsils, and a fulminating otitis. The throat culture showed streptococci. On the second day of illness two other children in the family developed scarlatina. The fact that this boy had had scarlatina when three years of age (with suppurating ears), made diagnosis by throat symptoms doubtful, but by the third day of illness he also had a well-developed rash over the chest and subsequent desquamation. Within twenty-four hours of initial ear symptoms the membrana tympani was freely incised and soon after pus flowed freely. The acute systemic symptoms subsided in a few days and thereafter his temperature was rather low for such extensive streptococcus invasion as followed. Early in the attack there was a very severe rhinitis with general edema of the nasal mucosa of both nares. It should be mentioned that there was persistent frontal headache early in the sickness but it was thought to be due to the mastoid inflammation, which is not rarely referred to this region. Sneezing was a prominent symptom. There was also marked photophobia. The gradual development of mastoiditis drew attention from the nasal symptoms, but there was a constant and copious sero-mucous discharge from both nares, which, however, did not become noticeably purulent until about the fifth week of sickness. In the meantime the ear condition progressed to suppuration in the mastoid cells, and complete mastoid exenteration was necessitated early in the third week. Fortunately there was no nephritis and no evidences of systemic disturbance followed, and for a week he did remarkably well. Frontal headache and photophobia subsided.

Then, in spite of apparently perfect postoperative conditions in the mastoid, the temperature, which had been near normal for a week, began to show a daily rise of 1 or 2 degrees. There was no discharge from the ear; in fact, hearing became normal ten days after operation and the patient progressed to complete healing of the mastoid in three weeks. The daily rise of temperature was coincident with the appearance of a mucopurulent nasal discharge from both nares. During the early period of the mucopurulent discharge from the nares there were no definite local symptoms of sinus involvement except intranasal edema in both ethmoidal regions. The patient was in excellent general condition, but daily fever persisted, maximum 101 F. The sinusitis on the right side gradually subsided. February 4 transillumination showed a very cloudy left maxillary antrum and left frontal sinus. I made diagnostic puncture into the antrum under local anesthesia, using Hartman's method, and irrigation washed out gelatinous mucopus.

Taking into consideration the impracticability of intranasal surgery, and that the right sinuses had apparently healed spontaneously, thorough treatment was given a trial before resorting to the radical operation. Rest in bed, application of epinephrin-cocain on cotton, warm saline douches with moist heat dressings, literally steaming the face and frontal regions for hours daily, was tried. The pus flowed more freely and there was less fever, but there gradually developed local frontal and maxillary tenderness, with marked frontal and maxillary edema. Orbital edema was not a pronounced symptom. The radiograph by Mr. Dachtler confirmed the diagnosis of purulent sinusitis of the left maxillary and frontal sinuses. The right frontal was in doubt, but the slight cloudliness was probably due to the previous inflammatory infiltration which was subsiding. Dr. Lasalle saw the patient with Dr. Van Pelt and myself and concurred in advising operation to relieve the empyema of frontal, ethmoidal and maxillary sinuses.

The radiograph showed a rather large sphenoidal sinus immediately behind the ethmoids, but there was no way of determining whether or not it was purulent.

Operation.—February 9, in the seventh week of scarlatina, assisted by Drs. Lasalle and Van Pelt, Dr. C. E. Price anesthetist, at St. Vincent's Hospital, I operated by the Killian method, adapted to the acute suppurative condition. The maxillary sinus was explored through the canine fossa. It was full of pus. A large opening was made, the cavity curetted clean of abundant granulation tissue and a free opening for subsequent drainage made into the naris below the inferior turbinate. The sinus was then firmly packed to prevent bleeding into the throat during the operation on the upper sinuses.

The frontal sinus was entered by making a curved incision from the region of the trochlearis, following the orbital margin and downward nearly to the lower edge of the nasal bridge. The periosteum was separated and the floor of the frontal sinus exposed. The trochlearis was not disturbed. Pus flowed freely from the frontal sinus. The bone was eroded in the lower part, and there was granulation tissue in the infundibulum of this sinus. The radiograph gave us perfect surgical landmarks, size of the sinus, location of septum between the two frontals, and it was cleaned out from below without opening above the ridge. The septum was intact. The ethmoidal labyrinth was thoroughly curetted to the depth of two inches from the frontal prominence. On the radiograph, lateral exposure, the sphenoidal cell was two inches from the frontal margin, but I am not positive that it was entered as it is difficult to discriminate between the posterior ethmoidals and sphenoid.

Up to this stage of operation the nasal mucosa had been kept intact, the object being to keep blood and pus from flowing into the throat. The last step was to enlarge the frontonasal duct and establish a large free opening from frontal and ethmoidal sinuses into the nose. This was done without sacrificing the middle turbinate. There was no shock and but little pain following the operation. On the second day all gauze packing was removed, and all of the sinuses were thereafter daily irrigated with warm iodin solution. The canine opening was closed in about a week and irrigation was thereafter made through the large accessory opening beneath inferior turbinate.

The amount of pus in the daily irrigations gradually decreased and by the third dressing the temperature was normal. On the fifth day it rose to 102 F., with apparently favorable local conditions and no systemic cause determinable. This continued for several days reaching 103 F., and autogenous vaccine treatment was decided on. A culture from the ethmoid granulations was used by Dr. T. B. Cooley in preparation of vaccines. The streptococcus vaccine was sterilized and standardized, 1,000,000 bacteria to the minim. There was febrile reaction following the first five minims (5,000,000) but thereafter very slight if any. At intervals of three or four days injections to the total number of seven were given, gradually increasing the dose up to 10 minims. The result observed during the first week of this treatment was decidedly favorable. As the nasal mucosa became normally sensitive ½ per cent. phenol normal saline solution was used. In four weeks all pus discharge had ceased, and the frontal sinus opening was perfectly healed with an inconspicuous but slightly depressed scar. The frontonasal duct remained patulous, the opening into the ethmoid cells could be seen and the accessory opening into the maxillary sinus was still open. Six weeks from date of operation the patient was in normal health, hearing normal, and even the sense of smell was not impaired.

It is evident from a critical review of this case that it could not be classified as the most virulent type of streptococcus infection. It was characterized rather by extensive invasion. The general condition was favorable (no nephritis) and it should be added that the boy had the very best of nursing. This, combined with perfect hygienic conditions,

was a factor in maintaining resistance. The temperature was not as high as would be expected in such extensive suppuration; in fact, there seemed to be an antifebrile toxic factor. The absence of severe cervical glandular infection was undoubtedly a factor in establishing a rapid and complete convalescence.

The question of serum or vaccine treatment of scarlatina is naturally introduced into this discussion. This disease is one that often taxes, I might better say, overtaxes, our therapeutic resources, and while the new treatment may be said to be in the experimental stage, yet there is sufficient encouragement to justify a thorough trial with the purpose of fortifying the system to resist the early toxic influences, and in the later stage to prevent the septic complications which are characteristic of this disease. The fact that this patient had had scarlet fever in infancy adds another complicating factor in the attempt to draw conclusions as to the merits of the vaccine therapy. Any treatment that will check suppuration in scarlatina will aid not only in preserving the function of organs involved, but also in preventing the spread of the disease, as it is a well-established fact that the discharges, and particularly nasal pus, is a carrier and disseminator of this contagium.

The advisability of the early use of autogenous vaccine treatment with the purpose of preventing sinus empyema in such a case as this is a subject for consideration. My own opinion is that the treatment was indicated early in the course of the disease—that is, prior to the development of empyema, with a possible chance of averting such an extensive operation. The second period of election was precisely as described—that is, soon after the operation, with perfect drainage established. Certain it is that convalescence was rapid and the sinuses were restored to normal in an unusually brief period, taking into consideration the extent of the empyema and that this boy had been sick in bed for nearly three months.

The early diagnosis of accessory sinus infection in the exanthemata deserves most careful attention and by timely treatment aided by vaccine therapy at the proper stage, and the radical operation if necessary, scarlatinal accessory sinus empyema may develop a surgical record comparable to that of the mastoid complications of this disease.

Nicholas Building.

STUDIES IN THE METABOLISM OF ATROPHIC INFANTS*

CHARLES A. FIFE, M.D., AND BORDEN S. VEEDER, M.D.
PHILADELPHIA

The value of a food for an infant depends, in the broadest sense, on two factors: on the one hand, whether or not the food meets the requirements of the organism in furnishing sufficient energy and material for growth, and on the other, whether or not the food itself, or the substances derived from it in the process of digestion, exert any deleterious action on the organism.

Fundamentally associated with the first problem is the question of absorption of the food in the gastro-intestinal canal. In our system of infant feeding in which the percentage of protein, fat and carbohydrate in the food is the criterion by which we judge of its suitability, and by which we modify the mixture according to the clinical manifestations, it is important to know whether the absorption of the different substances is influenced by the percentage relation of one to another. Very few observations have been made on this point. The following studies on atrophic infants were undertaken with the purpose of determining the absorption of fat under the influence of different proportions of fat and carbohydrate, and the influence of the varying quantities of fat and carbohydrate on the nitrogen metabolism.

The methods used were as follows:

The infants were given a definite formula for periods of at least six days, and during the last three days of each period the urine and feces were completely collected. The fat and nitrogen content of the food was determined each day during the periods by analysis. As the carbohydrate excretion was not considered, the sugar intake was not accurately determined, but was computed from the average found in many previous analyses of milk, plus the amount of a 1 per cent. lactose solution added to bring the formula to the desired strength. As will be seen later, it was only necessary to know the approximate quantity of sugar, i. e., whether the sugar percentage was high or low. The urine was preserved by chloroform and kept on ice until the three-day specimen was completed. The total three-day specimen of feces was evaporated to dryness in the usual manner. By using a three-day period after giving the same formula from three to six days previously, the chances of error from irregular excretion,

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*From the William Pepper Clinical Laboratory, University of Pennsylvania.

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TABLE 1.—DATA CONCERNING EXPERIMENT IN CASE 1 TO DETERMINE FAT ABSORPTION

Date	Milk Formula	Fat, gm.	Sugar, gm.	Protein, gm.	Amt. each feeding ounces	No. of feedings	Beginning weight	End weight
			PERIOD I					
2/27 to 3/4	3.5—6.5 —2.5	135.	235.	83.	6	7	10 lbs. 9 oz.	10 lbs. 11 oz.
Stools yellow, soft, mushy; no curds.								
			PERIOD II					
3/4 to 3/10	3.2—1.75—2.	115.	68.	57.4	8	7	10 lbs. 11 oz.	10 lbs. 11 oz.
Stools yellow, formed; no curds.								
			PERIOD III					
3/10 to 3/16	1.2—6. —2.5	57.	80.	89.28	7	7	10 lbs. 11 oz.	10 lbs. 15 oz.
Stools yellow, fairly well formed; few small white curds.								
			PERIOD IV					
3/16 to 3/22	1.2—6. —2.5	57.	273.4	89.28	7	7	10 lbs. 15 oz.	11 lbs. 2 oz.
Stools semi-liquid, greenish, few rather large white curds.								

TABLE 2.—DATA CONCERNING EXPERIMENT IN CASE 2 TO DETERMINE FAT ABSORPTION

Date	Milk Formula	Fat, gm.	Sugar, gm.	Protein, gm.	Amt. each feeding ounces	No. of feedings	Beginning weight	End weight
			PERIOD I					
2/27 to 3/4	3. —6. —2.	141.	270.	76.5	7	7	11 lbs. 10 oz.	11 lbs. 14 oz.
Stools soft, liquid yellow; no curds.								
			PERIOD II					
3/4 to 3/11	3. —2. —2.	145.8	80.	67.1	7	7	11 lbs. 14 oz.	12 lbs. 3 oz.
Stools liquid, yellow; no curds.								
			PERIOD III					
3/11 to 3/16	1. —2. —2.5	57.	80.	89.28	7	7	12 lbs.	12 lbs. 1 oz.
Stools soft, semi-liquid, greenish-yellow.								
			PERIOD IV					
3/16 to 3/22	1. —6. —2.5	137.	273.56	89.28	7	7	12 lbs. 1 oz.	12 lbs. 6 oz.

as at times occurs in twenty-four-hour specimens, are largely eliminated. *It is to be especially noted that the figures throughout represent the combined total of three consecutive days and not the daily intake or excretion.*[1]

The histories of the cases studied and the notes of the different periods are as follows:

CASE REPORTS

CASE 1.—Albert H., white, aged 9 months, was admitted to the hospital early in January for acute bronchitis, which cleared in a few days; previous history of gastro-enteritis and malnutrition; bottle-fed (milk modifications unknown) since shortly after birth; father tuberculous and mother mentally deficient. On admission the child weighed 10 pounds, 7 ounces, and at the time of beginning the studies was nine months old and weighed 10 pounds, 8 ounces. During the intervening two months the weight remained almost stationary, although numerous milk modifications were tried. The stools were soft, greenish or yellow in color and contained occasional curds. Physical examination showed a child with flabby musculature and little adipose tissue; cannot sit alone; length 25 inches; circumference of head 16 inches; circumference of chest 15½ inches; circumference of abdomen 15 inches; anterior fontanelle open, measures 1¼x1½ inches; superficial lymph-nodes slightly palpable; slight beading of the ribs; heart and lungs negative; abdomen soft and not distended; reflexes normal.

CASE 2.—Edward, white, aged 10 months, was admitted to hospital January 8 for diarrhea and loss of weight, with a previous history of malnutrition with loose and offensive stools. The child was bottle fed after two months; had diphtheria at four months followed by discharging ear; family history negative. On admission he weighed 10 pounds, 10 ounces. Under treatment the ear condition improved and the stools became much better in character, being as a whole yellow in color and smooth, with only occasional curds. The weight curve was fluctuating and between the time of admission and the first period the net gain was only one pound; age at time of beginning studies (Feb. 27), 10 months; weight 11 pounds, 10 ounces. Physical examination showed slightly rachitic, atrophic infant, with flabby musculature. He could hold his head upright, but could not sit alone.

Circumference of head 17 inches, chest 15 inches, abdomen 16½ inches. Anterior fontanelle open—1 inch in width; heart and lungs negative; liver slightly enlarged; umbilical hernia; posterior cervical lymph-nodes enlarged; reflexes normal.

FAT ABSORPTION

The work that has been done on the absorption of fats in infants is a difficult subject to review and correlate. There are apparently many discrepancies in the results of the studies of fat metabolism that have been published, which we believe in the first place depend largely on the methods used. Kumagawa and Sutro[2] have recently studied this question, using known quantities of fat, and find considerable differences in

1. Fat in the milk was determined by the Leffman-Beam method and nitrogen by Kjeldahl. The nitrogen of the urine and of the feces was determined by the Kjeldahl method, and Ca by the method of McCrudden. In the fat extraction from the feces the method of Brugsch was used, which permits of a separation of the soaps from the neutral fats and fatty acids.

2. Kumagawa and Sutro: Biochem. Ztschr., 1908, viii, 337.

the results obtained by several of the methods in common use. They have worked out a method which gives the most accurate results for total quantities of fat, but which does not permit of a separation of the fat in the feces into its component parts; i. e., neutral fats, fatty acids, and soaps. This is of considerable importance in the study of the feces in infancy, as it is supposed to bear an intimate relation to the question of the diseases of salt metabolism (rachitis, tetany, exudative diathesis, etc.). While the method we used gives results which probably vary from 5 to 10 per cent. from the total quantity of fat, the same error is carried throughout, and as the studies are comparative in nature this error is of little importance. It is also difficult to contrast the results of one worker with those of another, for although the studies as a whole are numerous, the conditions under which they have been undertaken differ considerably and the investigations are few in which any one point or question has been under consideration. A normal breast-fed or artificially-fed infant absorbs the larger part of the ingested fat. Bahrdt,[3] in the most recent and careful studies that have been made, using the Kumagawa method, finds an absorption of 93 per cent. in the normal child. A few years ago Freund[4] reviewed the various studies on fat absorption and from these and others since published it may be concluded that the normal absorption in a healthy infant lies between 90 and 95 per cent. The figures outside of these limits published as "normal" are probably due to either faulty methods or to disturbances in absorption. In both acute and chronic nutritional disturbances absorption of fats in the intestine is lowered, from 10 to 50 per cent. or more of the amount ingested being found in the stool. Practically all of this fat is derived directly from the food, a very small amount of ether-extractable substances being found in the stool with a fat-free diet. The loss of fat in nutritional disturbances is due to several factors, as altered digestion, accelerated peristalsis, admixture with mucus, etc. In our own cases the loss was from 15 to 33 per cent. of the quantity ingested. There is some question as to the form in which the fats are absorbed from the intestinal canal, but it is the generally accepted view that they must be split before absorption and are then recombined in the cells of the intestinal mucosa.

Our problem, however, did not deal so much with the question of how much was absorbed, or the form in which it was absorbed, as with the question of the absorption of large and small quantities of fat, and the influences of varying quantities of carbohydrate on the absorption of the fat. The accompanying table (Table 3) summarizes our results as regards the first question.

3. Bahrdt: Jahrb. f. Kinderh., 1910, lxxi, 249.
4. Freund: Ergebn. d. inner. Med. u. Kinderh., 1909, iii, 38.

TABLE 3.—SHOWING THE PERCENTAGE OF FAT LOSS IN THE TWO EXPERIMENTAL CASES DURING THE FOUR PERIODS

	Fat in Food Gm.	Fat in Feces Gm.	Fat Loss Per cent.
Case 1—			
A Period I	135	20.08	14.9
Period IV	57	18.89	33.0
B Period II	115	21.21	18.0
Period III	57	14.05	24.6
Case 2—			
A′ Period I	141	23.18	16.5
Period IV	57	18.86	33.0
B′ Period II	145	29.53	20.2
Period III	57	18.95	33.0

When large quantities of fat are given the actual amount of fat in the stool is increased but the percentage absorption is much better. Average figures show this clearly.

	Per-Cent. of Fat in Mixture	Fat in Food Gm.	Fat in Feces Gm.	Fat Loss, Per Cent.
Case 1	3+	125	20.65	16.0
	1	57	16.47	28.9
Case 2	3+	143	26.36	18.4
	1	57	18.90	33

In the 3 per cent. mixtures nearly five-sixths of the ingested fat was absorbed, while in the 1 per cent. mixtures a third was passed in the stool. Or, looking at it from another view-point, although there was about two and one-half times as much fat present in the food in the high fat periods, the feces contained only half again as much as in the low fat periods.

Somewhat similar results were obtained by Hecht[5] in a 12-months-old child in two three-day experiments:

	Fat in Food Gm.	Fat in Feces Gm.	Fat Loss Per cent.
Period I	89.28	4.929	5.3
Period II	10.26	1.662	16.3

In this case, however, there was considerable stimulation of the intestinal mucosa when the low fat was given (Milchmalzsuppe made with Magermilch). During this period the child passed from five to six liquid stools daily and the two investigations may have different interpretations although similar in results. L. F. Meyer[6] likewise observed a difference in proportion between the fat intake and the loss in the feces (normal child):

	Fat in Food Gm.	Fat in Feces Gm.	Fat Loss Per Cent.
1.	10.97	0.8	2.29
2.	35.95	1.588	4.44
3.	44.3	1.75	3.95

5. Hecht: Wien. klin. Wchnschr., 1907, xx, 497.
6. Meyer, L. F.: Biochem. Ztschr., 1908, xii, 422.

Freund[4] gives a similar comparison between normal infants:

	Fat Ingested Daily, Gm.	Fat in Feces Gm.	Fat Loss, Per Cent.
Experiment 1—			
Period I	3.93	0.4468	14.27
Period II	16.50	2.4160	14.64
Experiment 2—			
Period I	3.17	0.5785	18.25
Period II	15.90	2.2590	14.21

In this case the fat loss in the feces bears the same percentage relation, with high and low fat intake. There are so many points of difference (age, method, time, etc.) between our observations and those of Freund that we do not wish to draw conclusions from a comparison between the two.

As fat and carbohydrate differ from protein, in that they may be substituted for one another within certain limits, as both are energy and heat producers rather than tissue builders, we combined high and low carbohydrate diets with the fats in order to determine whether the amount of carbohydrate exerted any influence on the absorption of fats. Thus in Table 3 in the periods grouped under A and A′ the food contained a high (6) percentage of sugar. In those grouped under B and B′ the food contained a relatively low (2 per cent.) amount. The total amounts are given in the accompanying Table 4.

TABLE 4.—HIGH AND LOW CARBOHYDRATE DIETS COMBINED WITH FATS TO DETERMINE INFLUENCE OF CARBOHYDRATES ON FAT ABSORPTION

	Gm.		Gm.
Case 1—			
A Period I	235	B Period II	68
Period IV	273	Period III	80
Case 2—			
A′ Period I	270	B′ Period II	80
Period IV	273	Period III	80

Contrasting A with B, and A′ with B′ in Table 3, and considering the marked difference in the amount of carbohydrates in these periods, we are unable to find any apparent influence of the amount of carbohydrate on the absorption of the fat. Practically the same relation holds between the intake and absorption of large and small quantities of fat no matter whether a large or a small quantity of carbohydrate is present in the food.

As the quantity of nitrogen (see Table 6) in the food was nearly the same in all of the periods the explanation of these changes then must lie in the digestion of the fat itself. In no period was there a diarrhea present which might have accounted for the conditions. Moreover, the tolerance for or ability to absorb fat does not seem to be affected. In Case 1 there was an absolute absorption of 115 gm. of fat in Period I, while in Period IV the total quantity given was only 57 gm., of which a third (18.86 gm.), was found in the stool, only 1.2 gm. less than in the

first period. A similar condition was present in Case 2. In none of the periods was the so-called "soap stool" of Czerny's "milk injury" or Finkelstein's "balance disturbances" present. We investigated, however, the question of soaps and calcium excretion and the results are shown in Table 5.

TABLE 5.—SHOWING DETERMINATION OF SOAPS AND CALCIUM

	Milk Formula	Fat in Stools .... Gm.	Soap .... Gm.	Soaps Per .. Cent.	Ca .. Gm.
Case 1—					
Period I	3.5—6—2.5	20.08	2.57	12.3	3.54
Period II	3.2—2—2.	21.21	2.00	9.4	2.51
Period III	1. —2—2.5	14.05	6.13	43.6	2.51
Period IV	1. —6—2.5	18.89	6.30	33.3	3.95
Case 2—					
Period I	3. —6—2.	23.18	3.58	15.2	3.54
Period II	3. —2—2.	29.53	2.29	7.4	4.21
Period III	1. —2—2.5	18.95	10.66	56.2	3.72
Period IV	1. —6—2.5	18.86	9.90	52.5	3.74

In both cases the absolute quantity of soaps was about three times more in the low fat periods than in the high, and the relative amount was increased on an average nearly five times. The amount of Ca excreted in the feces bears no relation to the absolute amount or relative proportion of soaps. If in these cases the infants were atrophic as a result of fat injury, the high fat periods should have shown the higher amounts and percentages of soaps. An explanation on these grounds, then, is wanting. Birk and Rothberg thought the formation of fat stools depends on the withdrawal of the earthy alkalies through their combination with fat, and they see in this withdrawal the cause of the failure to gain weight in this condition. Freund contends that the amount of soap formation depends on the reaction of the stool, which in turn depends on the bacterial changes producing fermentation when large amounts of sugar are present. A study of Table 5 shows that in Periods I and II, with a high and a low sugar intake, the soap formation was low, and that in periods III and IV, with a low and a high sugar intake, the amount of soap is high, averaging 48 per cent. (Case 1) and 54 per cent. (Case 2) of the total quantity of fat in the stools. Moreover, the amount of Ca in the feces does not bear any relation to the amount of soaps present, whether we compare it with the actual amounts of soap or the percentage relation to the total amount of fat.

We must conclude, then, that the changes are due to certain unexplained factors and that they do not support any of the above mentioned studies on fat metabolism in chronic nutritional disturbances.

NITROGEN METABOLISM

The second part of the study took up the question of the nitrogen metabolism under varying fat and carbohydrate percentages and in this we have confined ourselves to the nitrogen retention. It is a generally

accepted fact that the amount of nitrogen in the feces is not proportionate to nor dependent on the amount of nitrogen in the food, although when increasing the food nitrogen from a very low or hungering period there is an increase of nitrogen in the feces. In investigations made by Kellar[7] on fasting infants an excretion of nitrogen in the feces of .0716 gm. and of .097 gm. in twenty-four hours was found after a preliminary period of thirty hours. In artificially fed infants the nitrogen amounts from 2 per cent. to 6 per cent. of the total weight of the dried feces.[8] Very little if any of the ingested nitrogen of the proteins is excreted as such although some of the nitrogen occurs in the form of their cleavage and putrefactive products. This together with the nitrogen of the gastro-intestinal juices and secretions, bacteria and epithelial cells, constitute the sources of the nitrogen of the feces. Although not directly dependent on the ingested food, it may be modified to some extent by the action of the food in stimulating or retarding the secretion of the gastro-intestinal juices, as the observations of Wohlgemuth and others have shown. It is very probable that, as in the case of Ca salts, the nitrogen absorbed may be excreted and reabsorbed in the intestinal canal. A glance at Table 6 shows no evident relation between the varying percentages of the food elements and the amount of nitrogen in the feces (i. e., nitrogen absorption). In Case 1 the amount varies from 1.345 gm. to 2.460 gm., while in Case 2 it is uniformly about 2.5 gm. in all four periods. For these reasons a study of the absorption is of little or no value and the important question is the study of the nitrogen retention. The nitrogen intake and the output in the urine and feces is shown in Table 6. The balance is considered as retained nitrogen, no account having been taken of the amount excreted through the skin. This is a small factor and in all probability would have been parallel throughout the periods in each case. So far as we know the only studies that have taken this into account are those of Rubner and Heubner,[9] and Tangl.[10] The former found a loss of 0.189 gm. of nitrogen per day in a normal child and 0.0338 gm. in an atrophic infant, while the latter found an excretion of 0.044 in an artificially-fed infant.

The nitrogen retention may be studied in two ways, either the total percentage retention (Nutzungswerth) or the retention per kilo of body weight. The figures for the latter (last column, Table 6) have been divided by three so as to give the retention per kilo per twenty-four hours, in order to compare our figures with those of previous studies. It will be noted that in all of our periods the retention of nitrogen was very good. The nitrogen intake in all of the periods was higher than was

7. Kellar: Arch. f. Kinderh., 1900, xxix, 123.
8. Hecht: Die Feces des Säuglings, 1911, p. 24.
9. Rubner and Heubner: Ztschr. f. Biol., 1899, xxxviii, 315.
10. Tangl: Arch. f. d. ges. Physiol., Bonn (Pflüger), 1904, clv, 453.

TALE 6.—SHOWING NITROGEN INTAKE AND OUTPUT IN THE URINE AND FECES

Period	N in Food	N in Feces	N in Urine	N Retained	Per Cent. of N Retained	Retention per Kilo per 24 Hrs.
Case 1—						
I	13.460	1.345	5.080	7.035	52.2	.482
II	9.185	1.418	5.174	3.593	39.2	.246
III	14.285	1.968	7.812	5.505	38.8	.370
IV	14.285	2.460	6.506	5.239	36.6	.349
Case 2—						
I	12.243	2.144	4.340	5.759	47.0	.351
II	10.722	2.550	5.660	2.512	23.4	.152
III	14.285	2.438	6.930	4.917	34.4	.298
IV	14.286	2.610	4.700	6.975	48.8	.416

necessary for the development and replacement of the body tissues. Although it was our intention to have the nitrogen intake the same in all periods, the total amount by analysis was less in Period 2 in each case. In both of these periods the absolute retention is less although the percentage retention in Case 1 is practically the same as in Periods III and IV. It is evident that an increase of the nitrogen in itself leads to increased retention, but this opens a question which is outside of the scope of the paper. The highest percentage and best absolute retention is found in the high carbohydrate periods (I and IV). This is seen clearly in Case 2 in which the retention in the high periods averages 48 per cent. and 29 per cent. in the low. In Case 1 it is less marked as the difference between the averages is only 5.4 per cent., although Period I shows the highest percentage retention of all—over half of the ingested nitrogen being retained in the body. This is not due to insufficient calories in the food in the low carbohydrate periods, as between 75 and 80 calories per kilo were present in the food in Period III, which is the lowest period from the standpoint of calories. This observation is in accordance with those of Kellar and of Orgler. Orgler[11] studied the influence of lactose and saccharose on the nitrogen retention in a normal child and his results are summarized as follows:

Food	Food-N	Urine-N	Balance	Per Cent. Retained
300 gm. milk	1.7748	1.2853	+0.229	12.9
250 gm. malzsuppe				
10 gm. lactose				
10+50 gm. lactose	1.6743	.6824	+0.583	34.8
10+50 gm. saccharose	1.8272	.8369	+0.663	36.3

Kellar's[12] case is less conclusive, as the kind of food was completely changed, although the carbohydrates were markedly increased and the nitrogen remained practically the same:

11. Orgler: Jahrb. f. Kinderh., 1908, lvii, 383.
12. Kellar: Malzsuppe, eine Nahrung für Magendarmkranke Säuglinge, Jena, 1908.

Food	Food-N	Urine-N	Balance	Per Cent. Retained
½ milk c.mm. water	2.6725	2.0274	—0.2646	9.9
Malzsuppe	2.3443	1.4463	—0.417	17.8

As regards the quantity of fat in the food, we may simply state that as far as these observations show it is without apparent influence on the nitrogen retention. In comparing the nitrogen metabolism of the atrophic infants with that of healthy artificially-fed infants we find a paucity of studies suitable for such purposes as a result of the variations in body weight and in the kind and amounts of foods used. The best suited for this purpose may be taken from Hoobler's[13] study of a nine months' infant weighing about 8 kilos. Three periods of three days each with a high, medium and low fat percentage, with a nitrogen intake of 20.7 gm., 21.6 gm., and 25.5 gm., respectively, were studied.

The nitrogen retention per kilo of body weight per day was as follows:

Low fat	0.362
Medium fat	0.270
High fat	0.285

Hoobler found that about 33 per cent. was retained in each of the periods; in other words, the amount of fat was of little influence. He thought the retention of nitrogen was not influenced by the amount ingested—a conclusion we do not feel is justified by his studies. Hoobler does not give the percentage of carbohydrate in his milk mixtures, but it is probable that they contained about 6 per cent. as is customary in most of the milk mixtures in this country. Comparing our periods of high (6 per cent.) sugar with his we find a much higher percentage retention as well as a better absolute retention:

	Case 1	Case 2
Period I	.482	.351
Period IV	.349	.416

The better nitrogen retention of the atrophic infants may be due to their beginning on a period of convalescence, as both children started in to improve from the moment they were placed on the metabolic bed in the first period.

SUMMARY

In the study of these two cases of infantile atrophy—the results of which are similar—the following conditions were noted:

The fat absorption was less than in normal infants, although the infants were able to absorb large quantities of fat.

The percentage absorption was better with a large amount of fat in the food than with low amounts.

13. Hoobler: Arch. Pediat., 1910, xxvii, 853.

The amount of carbohydrate in the food did not influence the fat absorption.

The amount of fat in the form of soaps in the feces was neither proportional to the amount of calcium in the feces nor to the amount of the carbohydrate in the food.

Both the actual and percentage amounts of soaps were greater when the fat intake was low.

The nitrogen retention was greater than in normal infants of the same age and weight.

Increasing the amount of the carbohydrate produced an increased nitrogen retention, but the nitrogen retention was not influenced by the amount of fat in the food.

2033 Locust Street.

A PREPARATORY STUDY OF THE BACILLUS ACIDOPHILUS IN REGARD TO ITS POSSIBLE THERAPEUTIC USE*

THOMAS MORGAN ROTCH, M.D., AND ARTHUR I. KENDALL, PH.D.
BOSTON

The recent advances in our knowledge of the biology of the gastroenteric tract have been so great that it seems time to begin a study of the practical use which can be made of individual organisms. Prominent among these organisms in the intestine is the obligate member of the acidoduric group, the *Bacillus acidophilus.*

It is to be noted in a general way that (1) this bacillus is a carbohydrate saprophyte; (2) it does not produce toxins; (3) it is a fermental organism, by fermental meaning an organism capable of breaking up the carbohydrates; (4) its habitat is the large intestine; (5) it thrives on carbohydrates, especially the sugars, such as dextrose, lactose and maltose; (6) it produces relatively large amounts of lactic acid from fermentable sugars; (7) it is antagonistic to the proteolytic organisms producing putrefaction, provided sugar is present; (8) although it produces acid it grows best when the medium is less acid; (9) it appears to grow better below the ileocecal valve than above; (10) it is of interest clinically because, under suitable conditions, when the host is placed on a carbohydrate diet, the organism becomes more abundant and it inhibits and even replaces to a considerable extent the bacteria characteristic of a protein regimen (this replacement of the protein flora by acidoduric bacteria is accompanied by the gradual diminution and even disappearance in the urine of those substances which are the products of protein decomposition in the intestine); (11) the *B. acidophilus* is non-pathogenic for experimental animals and under normal conditions is found to be an inhabitant of the intestinal tract of man; (12) it has the ability to render that portion of the intestine where it is localized unfavorable to the development of foreign invading bacteria, and (13) it can form a considerable amount of acid from carbohydrates, forming this acid mostly below the ileocecal valve.

In this same acidoduric group the *B. bulgaricus* has somewhat different characteristics. Its habitat is chiefly above the ileocecal valve, so that the acid which it produces must be transported to the large intestine and must act at a distance from the chief site of putrefaction and is, therefore, probably less effective than if it were generated at the seat of infection.

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Its action is most pronounced above the ileocecal valve and grows less as it approaches the anus and the bacilli are only sparsely found in the feces.

In contradistinction to the acidoduric group of intestinal bacteria are the proteolytic bacteria and their characteristics are suggestive of the antagonism which exists between the two groups. (1) The putrefactive (proteolytic) organisms attack and thrive on the protein elements of the food; in certain instances some may become invasive. (2) They may develop toxins. (3) The end products of protein break-down of certain of these organisms are found in the urine and appear as aromatic bodies, these bodies acting as evidence of proteolytic intestinal activity and in some measure acting as indices of such activity. (4) The habitat of this group is said to be chiefly in the large intestine and they are consequently more likely to be abundant below the ileocecal valve. (5) They flourish and increase best in an alkaline or neutral medium. (6) They are inhibited by an acid medium especially by the presence of lactic acid. (7) Certain of these proteolytic bacteria are facultative and as a rule when protein and carbohydrate substances are present they attack the latter first and spare the former. (8) The addition to the diet of easily fermentable carbohydrates, together with restriction of protein food, is of material assistance in reducing the output of these putrefactive products. This results also in the diminution of the activity of the bacteria producing them.

There appears to be a considerable number of intestinal disturbances associated with the activities of putrefactive bacteria, some of which may be influenced by the activity of the *B. acidophilus*. As a well-known example of such putrefactive condition we might mention bacillary dysentery. There are three prominent bacilli which are associated with the clinical symptoms of bacillary dysentery: *B. coli*, streptococci and *B. dysenteriæ*, one or both types. So far, however, as the clinical picture of bacillary dysentery is concerned a differential diagnosis between these organisms cannot be made. The actual recognition of which of these organisms is producing the disturbance is dependent on the bacteriologic examination. Hitherto bacillary dysentery has been regarded as a disease brought about solely by the action of the dysentery bacillus. Now, however, it appears in most cases, at least, that the three organisms mentioned above working symbiotically in appropriate intestinal conditions produce the symptom-complex of bacillary dysentery.

It is to be noted here that in those instances in which the acidoduric group of organisms has produced lactic acid in considerable amount (through the influence of a carbohydrate diet), *B. coli*, in virtue of its being a facultative organism, changes its metabolism from the proteolytic to the fermentative type. In consequence of this change in metabolism from the putrefactive to the fermentative type, this organism (*B. coli*),

which on the protein regimen produced putrefactive products inimical to the patient, and which was, therefore, a symbiote of the dysentery bacillus, now becomes an antagonist to it by forming lactic acid.

In like manner, although we do not know so much about the antagonistic action in this connection, it has been observed that the disturbing streptococci are lessened in number apparently by the action of the lactic acid. It has also been shown in regard to *B. dysenteriæ* that certain changes in its action are brought about by the influence of the change to the carbohydrate type of diet. These changes, so far as is at present known, are as follows: the bacillus, whether of the Shiga or Flexner variety, is normally of the proteolytic type, and, having gained entrance to the intestinal tract, locates itself chiefly below the ileocecal valve. It begins its attack on the protein in the intestine and produces toxins. The bacilli may penetrate the mucosa and even the tissues as far as the mesenteric lymph-nodes and thus establish the bacillus as an infectious organism. The toxins are absorbed and especially affect the anterior horns of the spinal cord.

It is evident that any beneficial therapeutic action on the infectious organisms, so far as the action of the acidoduric group on them is concerned, is to diminish their numbers and to prevent their production of toxins by rendering the medium in which they are growing unsuited for their continued development, thus reducing the amount of toxin which they produce. The damage brought about by the toxins already absorbed cannot be undone. Early inhibitory action of the acid-producing bacteria is therefore indicated.

It has been noted in the changes in flora which take place in the intestine, when by any means the putrefactive types of organisms are gradually changed to the fermentative type, that during the process the bacterial flora first returns practically to a normal type for the nursling, namely, to *B. bifidus* mostly, and to *B. acidophilus* to a degree. Then, as the carbohydrate of the diet is increased the acidophilus increases in number and greater amounts of lactic acid are produced. Care, however, must be taken not to allow the acidophilus to flourish to such an extent as to establish an acid intolerance in the host.

To be mentioned as of especial significance in an investigation of this kind are certain known possibilities in connection with influences which may be brought to bear on the intestinal flora, and changes which may be accomplished by varying the quality of the food presented to intestinal organisms.

The character of the intestinal flora of man, both with respect to the types of organisms represented, and to the nature of the resulting chemical activities, depends largely on the composition of the diet of the host. A moment's reflection will convince one of the accuracy of this statement; the intestinal bacteria, to a very considerable extent, derive their suste-

nance from the food in the alimentary canal, and as the food varies, so will the bacteria vary.

This variation in the nature of the bacteria comprising the intestinal flora can conceivably change in two distinct directions, following alternations in the host's diet: either the organisms representative, for example, of a protein regimen may be replaced by an entirely new flora when the host changes his diet to one potentially carbohydrate, or the bacteria characteristic of the protein flora can shift their metabolism to meet the new conditions established by the carbohydrate regimen. As a matter of fact, both possibilities are realized, so that we may recognize three distinct classes of bacteria when the food of the host varies from a protein to a carbohydrate diet. We recognize first an obligate proteolytic group of bacteria, which thrive on a protein regimen. These organisms, best exemplified by *B. putrificus,* are in reality to be regarded as bacteria characteristic of putrefactive conditions in the intestinal tract. They disappear largely when the food is changed to carbohydrate.

The second group, the obligate fermentative bacteria, grow best and are most numerous when carbohydrate forms a prominent part of the diet. These bacteria in virtue of the considerable amounts of lactic acid which they form under suitable conditions, are antagonistic to, and tend to replace, the obligate putrefactive (proteolytic) bacteria. *B. acidophilus* is the best known of this group. The third group, the facultative organisms, are those which accommodate, within limits, their metabolism now to a protein, now to a carbohydrate regimen. They are usually present in either class of food but are more numerous on the protein type of regimen, because they are less affected by the products of putrefaction, than those of fermentation. *B. coli* and *B. proteus* are perhaps the best known of the facultative group.

We recognize, then, three well-defined types of bacterial activity in the intestinal tract, the putrefactive or proteolytic type, acting on the protein, the fermentative type acting by preference on carbohydrate, and the facultative type, which is by far the largest and best known, acting either on protein or carbohydrate.[1]

It is interesting and particularly important to recognize that the intestinal bacteria of normal nurslings are strictly fermentative. This is what one would expect, because the diet of the nursling is one well suited to encourage a fermentative flora, being composed of over 6 per cent. lactose and only about 1.5 per cent. protein. The reaction of a normal nursling's feces, furthermore, is strongly acid, due to the formation of lactic acid within the intestinal tract by this fermentative flora. It will be seen later on that this lactic acid, formed by the activity of

1. For a fuller discussion of these types, see Kendall, A. I. "Lactic Acid Bacteria: What They Are and What They Are Supposed to Do." Boston Med. and Surg. Jour., 1910, clxiii.

fermentative organisms, is an important feature in keeping down putrefaction. In this connection it should be stated that the flora of normal nurslings contains few, if any, putrefactive organisms. As the child grows older and is placed on a cow's-milk diet, a change takes place in the intestinal flora: this change occurs less rapidly if the diet is strictly limited to modified milk, more rapidly if the diet is made up of unmodified milk or with the addition of protein. The change consists essentially in the replacement of the characteristic fermentative flora of the breast-fed baby by greater or lesser numbers of putrefactive and facultative bacteria. It is marked by the beginning dominance of the facultative bacteria which tend to persist throughout life.

The cause underlying this change is not difficult to define: the change in flora is largely attributable to the relative decrease in carbohydrate, associated with the increase of protein, two conditions favoring the development of a putrefactive or facultative flora.

It may be accepted as proved that the fermentative flora of the normal nursling is a valuable factor in protecting the host from invasion by foreign organisms, particularly of the proteolytic type. Consequently the lack of such a flora is to be regarded as a weakness in the normal defence against bacterial invasion of the intestinal tract. It has been shown for example[2] that the intestinal flora in bacillary dysentery is essentially putrefactive in nature, at least in the more severe cases. It would appear logical and desirable, then, to attempt to reestablish and maintain the fermentative conditions at least in the intestinal tract of babies, and thus to encourage the reestablishment of the normal fermentative flora characteristic of such cases.

The question arises: How may this be accomplished? From what has been said it is evident that the increased administration of carbohydrate, and the restriction of protein will furnish the dietary conditions most favorable for the development of the appropriate organisms, and if the bacteria in question, the obligate fermentative bacteria, are present, and available in the intestinal canal, they may be brought up to their natural degree of activity. This process, however, takes a certain amount of time, and conditions may well arise in which the amount of time necessary to bring about this bacterial change will be prohibitive. For such cases, where time is a factor, and where it is desirable to populate the intestinal tract with useful types of fermentative organisms, the use of artificially prepared cultures of appropriate organisms is indicated, provided they can be obtained.

The observations presented in this paper are designed to show the feasibility of encouraging the growth of *B. acidophilus* by suitably modifying the food of the patient; if, however, acidophili are not present in

2. Kendall, A. I.: Bacillary Dysentery, Boston Med. and Surg. Jour., 1911, clxiv, 288.

the alimentary tracts of patients, it is apparent that they cannot be encouraged to grow even by the most careful dietary regulation. In such cases we deem it advisable, from the theoretical point of view, to introduce cultures of acidophili, provided they have been obtained from sources known to be normal and absolutely free from objectionable conditions.

The characteristics of this organism (*B. acidophilus*) have been described fully in a previous communication[3] and need not be repeated here.

Cultures were readily obtained from two different patients by feeding maltose or lactose in moderate amounts. The details of the feeding experiments appear below.

The patients were first put on a diet in which protein was in moderate excess, and the characteristic protein flora dominated, as is shown by the protocols. As the diet was gradually changed to one in which carbohydrate predominated, there was a gradual restriction of the proteolytic flora, the more strictly proteolytic organisms diminished in numbers and the bacteria characteristic of the carbohydrate regimen, *B. bifidus* and *B. acidophilus,* gained the ascendency. These changes are of more than academic interest, for they indicate a possible method for controlling the proteolytic organisms, to a certain extent, at least, by dietary changes that are not only not harmful, but even under certain conditions beneficial to the host. While we are still quite in the dark concerning the absolute amount of importance to attribute to the presence of a more or less purely protein flora, the evidence is strongly in favor of the view that these organisms may not only be harmful themselves, but also that they may, and probably do, thrive in conditions suitable for the development of organisms like the typhoid or dysentery bacilli. On the other hand it is equally true that the conditions obtaining in the intestinal tract favorable for the continued development of the fermentative flora are inimical to the development of these pathogenic bacteria as well as for the putrefactive bacteria. Indeed, it appears to be a fact that the pathogenic organisms of the typhoid type, for example, are rather less resistant to the acids of the fermentative bacteria than are the more commonly met-with putrefactive bacteria which occur from time to time in the intestinal tract.

It is not a matter of indifference which fermentative bacteria are encouraged to develop in the intestines; furthermore, certain organisms appear to elect the small intestine, others the large intestine. As a well-known example of the former, *B. bulgaricus* may be mentioned, while *B. acidophilus* is found most plentifully in the large intestine. Applying these principles clinically, it would appear that putrefactive conditions in the small intestine might be controlled more readily by an organism that

3. Kendall, A. I.: Jour. of Med. Research, 1910, N. S., xvii, 153.

generated lactic acid in that portion of the alimentary canal, and *B. bulgaricus* would be selected for this purpose, while *B. acidophilus* theoretically, at least, would be more promising for putrefactions of the large intestine.

We have shown that *B. acidophilus* was increased in numbers on the sugar diet, and this method of encouraging the growth of this organism would appear to be relatively simple. The time necessary to bring this increase in *B. acidophilus,* however, varies considerably and doubtless depends on the numbers and activity of the organisms of this type remaining when the carbohydrate regimen is instituted. There are cases in which it would be desirable, or even essential, to be able to introduce large numbers of acidophili with the minimal expenditure of time, and we believe that artificial cultures of this organism are indicated. The problem arises: Is it possible to cultivate *B. acidophilus* in artificial media and still have it retain its desirable properties? Further studies on this point are needed before the question can be definitely decided.

It is evident from what has been stated that it is worth while to investigate whether the inhibitory action of *B. acidophilus* on certain harmful proteolytic organisms can be made use of therapeutically, and it is with this object in view that we have done some preparatory work on this subject. The first step in an inquiry of this kind is to obtain a strain of the acidophilus which has been shown to fulfil certain requirements, just as has been seen done with *B. bulgaricus.* This strain should be kept in pure culture ready for use according to the physician's demand.

After a series of investigations our interests centered on the following two cases which seemed to well illustrate how we obtained vigorous specimens of the *B. acidophilus* by carrying out suitable modifications of the diet according to the principles which we have described. These cases illustrate, furthermore, in a striking manner the alternations in the types of the fecal bacteria following the changes in diet. It is to be noted in studying the bacterial changes in these cases that *B. acidophilus,* like other bacteria, is selective of the kind of sugar that it prefers and thrives on, and that it is apparently encouraged to a greater degree of activity in a medium containing dextrose or maltose than any other sugars.

CASE REPORTS

CASE 1.—A boy, 6 months old, was being fed on a milk mixture containing a low protein, and for its sugar, lactose. The feces showed a moderate number of proteolytic organisms. On March 9 a high protein (3.50) was given and on March 13 the report of the feces was: Yellowish brown, with small curds; no mucus; slightly fetid odor. Bacteria: *B. coli, B. subtilis,* a few coccal forms; rather typical putrefactive feces both culturally and morphologically; practically no acidophili; many gelatin-liquefying forms. The food mixture was then changed to a low protein and the lactose replaced by a moderate amount of maltose—5 per cent. March 17 the report of the feces was: Yellow, with greenish color on the exposed parts; relatively homogeneous; odor not distinc-

tive; *B. coli* and *B. subtilis* less in numbers; acidophili present in moderate numbers; a few bifid forms and a very small number of coccal forms appear; liquefying organisms greatly reduced in numbers and in activity. The maltose was then increased to 7 per cent. and the report on March 22 was: Yellow, granular and dry; *B. coli* and *B. subtilis* have almost disappeared; very few coccal forms persist; acidophilus and bifid forms increased. On March 27 the report was: Yellow, granular and relatively dry; bifid forms and acidophili present in considerable numbers; very few proteolytes; liquefying forms greatly diminished. On April 8 the report was: Small in amount, light color, with greenish color on exposed surfaces. Proteolytic bacteria have almost disappeared. Culturally, very few liquefying forms are left; they are very inactive; acidophilus and bifid forms still dominate.

In this case a markedly putrefactive intestinal flora was gradually changed to a practically normal nursling's, and then to one markedly acidoduric by providing at first a protein diet and then carbohydrate. The acidophili were vigorous and were separated and kept in pure culture. They were used to coagulate milk but did not make an entirely satisfactory buttermilk. The reason for this appears to have been that the culture obtained at this time was less vigorous than those usually obtained under suitable conditions. This is in line with the well-known variations which different strains of the same organism not infrequently exhibit in artificial media.

Case 2.—A boy 17 months old, was being fed on a rather excessive protein diet and on March 13 a report of the feces was as follows: Greenish, homogeneous with a few small curds which were very hard; odor suggestive of putrefaction in intestinal tract (indol odor marked); culturally, *B. coli* few in numbers; many subtiloid organisms; a few coccal forms were present; liquefying forms numerous and active culturally; no acidophili found. The protein part of the diet was then decreased and on March 17 the report was: Light yellow, with slightly sour odor; good feces morphologically; *B. coli* still present in small numbers; *B. subtilis* present although in fewer numbers; liquefying colonies still active and numerous; practically no bifid forms or acidophili. The diet was then made largely carbohydrate and on March 22 the report was: Light brown, smooth, homogeneous; *B. coli* very few in numbers; *B. subtilis* greatly reduced, both numerically and in activity. Bifid forms appear in moderate numbers, together with acidophili; feces changing from the putrefactive to the fermentative type. On March 27 the report was: Brown, smooth, homogeneous; moderately voluminous; odor slightly sour; no starch demonstrable microscopically; culturally, very few *B. coli*, few *B. subtilis*, little liquefaction, and few liquefying forms; bifid forms in moderate numbers; considerable numbers of acidophilic bacteria; feces distinctly fermentative in type. On April 5 the report was: Smooth, brown, homogeneous; slightly acid reaction and sour odor; culturally, very few proteolytes were found and those that were recovered showed but little liquefying activity; bifid forms more numerous, acidophili dominant; typical fermentative feces.

In this case a markedly putrefactive intestinal condition was gradually changed under the influence of a carbohydrate regimen to a typical fermentative one. The acidophili were vigorous and were isolated and kept in pure culture. When introduced into milk the resulting lactic acid coagulation was exceedingly satisfactory and so this strain has been retained for further investigation.

Successive transfers must now be made with this strain of the acidophilus to see if it retains its useful properties of antagonism to the putrefactive conditions, which it has been shown to possess, or whether when used in milk it becomes acclimated and loses these properties. It is probable that it retains its strong lactic acid forming properties as does the *B. bulgaricus,* but if it does not it is possible that it may still be given therapeutically in a carbohydrate menstruum. If it can be given in this way it seems reasonable to suppose that the acidophilus will be superior to the bulgaricus in its power of inhibiting those putrefactive disturbances which are located below the ileocecal valve. It is here to be especially noted that while the activity of the bulgaricus grows less when it passes the ileocecal valve, that of the acidophilus increases, the latter always approaching in its downward descent its home, where it flourishes best, increases in number and vigor and produces most acid.

197 Commonwealth Avenue.

ANAPHYLAXIS IN ITS RELATION TO PEDIATRICS*

GODFREY R. PISEK, M.D., AND MARSHALL C. PEASE, M.D.
NEW YORK

That anaphylaxis has an important bearing on many of the fundamental problems of medicine is indicated by the numerous recent laboratory studies both in this country and abroad. A satisfactory explanation of the phenomena would doubtless clear up a large number of diseases, and this is especially true of those occurring in early life. Questions of anaphylaxis and immunity are closely associated, and a better knowledge of the former would lead to progress in the latter.

Auer and Lewis have demonstrated that the immediate cause of death in sensitive guinea-pigs reacting to a second injection of antigen is asphyxia, due to tetanic contractions of the smooth muscles of the bronchioles, and that this contraction is probably peripheral rather than central in origin. Schultz has in a measure confirmed this view by showing that horse serum acting *in vitro* on excised smooth muscle fiber from a guinea-pig sensitized to horse-serum causes a contraction which is much more marked than when acting under the same conditions on the same tissues from a normal guinea-pig. While this action on the respiratory function is the most striking phenomenon of anaphylactic shock, there are a few other well-proved clinical symptoms. Pfeiffer claims that the most constant and delicate symptom of anaphylactic shock is a marked fall in temperature. That there is a fall in blood-pressure during the time of anaphylactic shock, both in guinea-pigs and dogs, has been repeatedly demonstrated. Biedl and Kraus, and Arthus have shown that another characteristic of the anaphylactic reaction is a decrease in the coagulability of the blood, while Michaelis, Fleishman, Slieswijk, Friedman, Friedberger, and Hartoch have demonstrated a measurable decrease in the complement content of the blood.

The symptoms, then, of the anaphylactic reaction are asphyxia, falling temperature, decreased coagulability of the blood, and an actual loss of complement. The heart continues to act for some time after the respirations have ceased.

While working on this problem and confirming some of the laboratory experiments, with a view to their clinical value, our attention was attracted by the marked parallelism of these anaphylactic symptoms and those described by Goodall, an eminent obstetrician and gynecologist of McGill University. He reported three cases of sudden death of infants

*Read by invitation before the New England Pediatric Society, May, 1911.

which came under his observation. As he expresses the hope that his report of these cases "may draw forth evidence from other sources, either to corroborate or refute his conclusions," we shall use his material freely as a starting point for our discussion of anaphylaxis.

Goodall's three cases were practically identical. The mothers suffered from a more or less severe postpartum eclampsia. The children, after their first "copious nursing," were seized with convulsions. The clinical picture is presented as follows: "Duskiness, cold extremities, blue nose, shallow, irregular respirations, and muscular rigidity from time to time in the lower extremities." Death in each case was due to respiratory failure; the heart continued to beat long after artificial respiration was instituted. There was no vomiting nor nausea. Emphasis is placed on the fact that these children were considered absolutely normal.

These cases are discussed by him with a view to answering the question whether an eclamptic mother should nurse her newly-born child. He asks: "Were these children healthy, and if not, what was the nature of their illness? Was there a toxin in the mother's milk which was fatal to them?" These are all questions which would naturally suggest themselves.

After reviewing the literature on the subject, he comes to the conclusion that many of the children born of eclamptic mothers have lesions of the kidneys, and therefore he considers that these apparently healthy children, to use his own words, "are far from being healthy." That he feels that this conclusion is inadequate is shown by the fact that he seeks another cause by affirming that the milk of an eclamptic mother is in itself toxic for her child. This toxin, he believes, is derived from the fetus and appendages. He attributes the eclampsia to the pregnancy, and the cure is the removal of the fetus with its appendages. Eclamptic attacks seldom, if ever, come on without uterine contractions having set in, resulting in pumping into the general circulation a large amount of toxins. It is these toxins, he concludes, which caused the death of these children, and this was the more easily brought about because the children were not as normal as they seemed.

We have given Goodall's explanation of the cause of death in these three cases in some detail, for the reason that they do and do not explain. The supposition of a possible kidney complication is not tenable, as the children were born healthy and remained so until after the first nursing. They showed no symptoms of kidney disease, and the convulsive seizures were not like those of nephritis.

That the mother's milk was in some way at fault seems certain. The attack came on shortly after the first "copious nursing," and clinically was the same as that in anaphylaxis. The symptoms were typical, and can easily be duplicated in the laboratory. The similarity to the symptoms of anaphylactic death is to be noted. The exitus was due directly

to respiratory failure, the heart continuing to beat for a long time after the respiration ceased. There was also a fall in temperature. It would be interesting to know whether or not there was a fall in blood-pressure, but the only statement which in any way bears on this point is that the "pulse was slow and full."

Can the conditions as above outlined be duplicated in the lower animals? To bring about anaphylaxis in the lower animals, they must first be sensitized. The sensitizing agent is known as an antigen, and must be capable of causing the production of antibodies in the animal into which it is injected. In a general way these antigens belong to the group of either albumins or proteins. The reaction to this antigen is specific. For example, the same albumin or protein must be used for the second injection as was used to sensitize the animal. Rosenau and Anderson sensitized a series of guinea-pigs with guinea-pig placental extract, and after twenty-two days gave these sensitized guinea-pigs a second injection. Out of twelve guinea-pigs treated in this manner, eleven showed symptoms, and at least three had convulsions. These observations have since been confirmed by others. This series of experiments tends to show the possibility of sensitizing the mother with autolytic products of her own placenta. Goodall has specifically pointed out that eclampsia is always, or nearly always, preceded by uterine contractions, and these force into the general circulation the poisons which bring on the attack. Here we find all the conditions for an anaphylactic reaction duplicated. Uterine contractions, perhaps not noticed, have sensitized the mother; a continuation of the same process has forced into the general circulation a sufficient amount of the fetal products to bring about an anaphylactic reaction.

Can a child inherit its mother's sensitiveness to these toxins? Again, Rosenau and Anderson have proved that hypersusceptibility was transmitted through the female guinea-pig to her young; the male having no influence. This hypersusceptibility follows, whether the female guinea-pig is sensitized before or after conception, and is in no way dependent on the milk. These experiments prove conclusively that these children could have inherited susceptibility from their mothers.

Given the above conditions, the point still remains to be established as to whether or not it is possible to absorb a sufficient amount of unchanged protein or albumin through the gastro-intestinal tract to bring on a condition of anaphylactic shock. With a view to finding an answer to this question in our experimental work in anaphylaxis, four guinea-pigs were sensitized with whey, four with milk boiled two minutes, and five with untreated milk. Twenty-eight days later they all received 6 to 10 c.c. of milk mixed with carrots. All manifested at least mild symptoms, such as an increase in the rate of respiration and a desire to remain quiet in spite of disturbances which usually worried them consid-

erably. Four out of the thirteen lay down on their sides. One of the number died.

In nine other sensitized pigs, diarrhea was artificially brought on by the administration of croton oil, after which they were fed with milk. The results were as follows: four very sick; rapid respiration; lie down and get up; one died of convulsions; four remaining pigs act sick, but no more so than the controls; refused to eat; four used as controls were very quiet; none had convulsions or died; none refused to eat carrots.

The above series of our experiments makes it clear that in guinea-pigs, at least, it is possible to bring on an anaphylactic shock by absorption of milk through the gastro-intestinal tract.

We were able to confirm Rosenau and Anderson's findings to a limited extent, regarding the possibility of sensitizing guinea-pigs with placental extracts. The placenta was ground up and allowed to autolyze at room temperature for an hour, and some of the resulting extract was injected into two female guinea-pigs. A second injection of 6 c.c. was given ten days later, with the result that one guinea-pig had a convulsion from which it recovered at the end of half an hour; while the other, for the same length of time, was very quiet, lying over on its side and breathing very rapidly.

It is our intention later to report on experiments in which we attempted passively to sensitize a series of guinea-pigs with a blood-serum from an eclamptic woman, and then note if at the end of twenty-four hours an anaphylactic shock can be brought on. The same experiments with milk alone would perhaps be as valuable, though less conclusive. It has been shown that it is possible to sensitize the mother with placental extract; that this hypersusceptibility may be transmitted to her young; and, finally, that a sensitized animal can absorb a sufficient amount of antigen through the gastro-intestinal tract to cause a condition of anaphylactic shock.

Does not this series of experiments show that Goodall's three infants died of anaphylaxis? Experimental facts and the clinical data are in perfect accord, and we feel that histologic examinations would have brought to light no pathologic conditions to explain adequately the symptoms exhibited in these three cases.

The factors which were so fatally important in these infants, probably in a somewhat less degree, have a bearing on many of the feeding problems of infancy and childhood—more especially in those in whom there is an idiosyncrasy to some especial form of food. Intolerance for egg-albumin, buckwheat, various fruits (as strawberries) and vegetables (as celery) are well-known examples. Many atrophic children fail entirely to digest cow's-milk, no matter what the modification, their only hope of recovery being in furnishing them with human-milk. These conditions, as a rule, begin in moderate digestive disturbances, and it seems fair to

assume that a sufficient amount of unchanged milk-protein is absorbed to cause hypersusceptibility. It is well known that a quite constant concomitant symptom of this condition is a lowered body-temperature and a soft pulse. That these children do not rapidly die from convulsions or respiratory failure is due to the fact that there is a constant but small absorption of antigen. It is at the present time well recognized that an anaphylactic reaction may be entirely avoided or much decreased in severity by injecting into the general circulation minute quantities of the antigen before giving the second dose. The fact that these children so often recover when placed on human-milk, indirectly bears out this view. It is impossible to sensitize an animal with its own proteins; that is to say, a guinea-pig cannot be made hypersusceptible with the blood-serum of its own species. In the same way and for the same reason it would be impossible to cause an anaphylactic reaction in an infant with human-milk. If, on the other hand, milk from an animal of the same family is used, as for example a second injection of sheep's-milk into a guinea-pig sensitized with cow's-milk, we can obtain, in most cases, marked symptoms of an anaphylactic reaction. We should not expect, therefore, that a child who is doing poorly on cow's-milk would improve on milk from the same species of animal, while it might do very well for a time at least on milk from an ass. These observations suggest a difference in the protein matter of the milk of different species of animals. Of some importance also is the fact that infants quite regularly do well on almost any milk for the first week or ten days. Von Pirquet and Schick early in their studies on the so-called serum disease demonstrated the fact that there was an incubation period of from seven to nine days; and Rosenau and Anderson, in their work on horse-serum, found that guinea-pigs became susceptible to the second dose about the seventh or ninth day. This hypersusceptibility does not appear suddenly, but comes on somewhat gradually. Herein, perhaps, lies the explanation as to why it is that a milk mixture begins to disagree with a child at the end of about a week without any apparent cause.

While the recent studies in anaphylaxis have brought to light many facts which are at least suggestive in the field of infant feeding, there are other phenomena equally interesting when taken in connection with diseases common to children. Among these is the injection of animal serum into the human being for prophylactic or curative purposes. The sera which have been most commonly used are those which have been derived from the horse—as the antitoxin for diphtheria and, more recently, Flexner's serum in meningitis. These had not been long in use before certain clinical symptoms were noted; and occasionally even sudden collapse, with death in a few instances, resulted. The symptoms which followed the use of horse-serum are noteworthy in this connection, as in them are seen anaphylactic phenomena which in every way resemble

those which can be produced artificially in animals. The study of this artificially produced anaphylaxis in human beings was first reported in detail by von Pirquet and Shick, and the symptoms of their so-called "serum disease" are given as urticaria, fever, edema and pains in the joints. As has been indicated, the symptoms in serum sickness are usually mild, but occasionally there is severe dyspnea, asthmatic in type, and, rarely, sudden death. The first and best known of these tragic cases is that described by Langerhans.

"A child 1½ years old, received 2 c.c. of antitoxin subcutaneously. Before the injection the child was cheerful, but five minutes later he became restless, cried, and then began to have great difficulty in breathing. The skin over the whole body became cyanotic; finally there was a severe convulsion, the pupils becoming widely dilated, and foam appeared at the mouth. Seven minutes after the injection, the child was dead."

A number of such cases have been reported in the literature. The symptoms are always identical, and frequently the statement is made that the heart continues to beat long after respiration has ceased. While these instances of sudden death are intensely interesting, the symptoms of the milder types of the disease are still more so, as *they suggest an etiologic factor for a number of clinical conditions which at the present time are far from being clear.*

It has long been recognized that urticaria is closely associated with certain food idiosyncrasies, and that all types of the disease yield quickly to dietetic measures. It has been classed with eczema and angioneurotic edema as a form of "exudative diathesis." These diseases bear a marked resemblance to conditions which are occasionally associated with a second injection of antitoxin in children. While it has not yet been possible to produce experimentally skin lesions analogous to eczema, it is suggestive that therapeutically the disease is best treated by a radical change in diet, with especial care to increase the functional capacity of the eliminative organs. In any event, it would not be expected that experimental proof would be conclusive, as in a condition so chronic it would be necessary to carry on the work over a long period of time, which of itself would preclude obtaining any definite results in children.

Localized reactions to a second injection of antigen occur best in those animals which give the more generalized phenomena with the greatest difficulty. The only animal which regularly gives the general symptoms of irritation, paresis and respiratory failure is the guinea-pig. These generalized symptoms can, however, under proper conditions, be produced in all animals, including man, as has already been pointed out. This observation is an important one since it serves as an explanation of certain localized diseases. Arthus first noticed necrosis at the point of injection in rabbits. Lucas and Gay, some time later, made the same observation on human beings. Elliotson, as far back as 1831, traced the

cause of hay fever to certain kinds of pollen, and Blackley and Dunbar have rather recently confirmed this observation. They were able to produce this disease at will, even in the winter, by exposing individuals subject to hay fever to small amounts of pollen, whereas normal individuals do not react in the least under similar conditions. This reaction is not due primarily to an endotoxin, as Wolff-Eisner has suggested, but is a true, localized anaphylactic reaction. That this is not a constitutnoial idiosyncrasy is shown by the fact that children do not suffer from hay fever, the first attack appearing some time between the tenth and the twentieth years. However, some of the forms of asthmatic bronchitis show a type of reaction similar to that of hay fever.

Freiberger describes the case of a young man who was highly susceptible to horse-albumin. He could go about among cattle without developing any symptoms whatever, but as soon as he came near a horse he would be seized with asthma and have severe respiratory disturbances. This hypersusceptibility was so great that it was necessary for him to ride in the back seat of a wagon, and even then he did not always escape an attack. That these attacks were due to emanations from the horse was shown by the fact that he was much less liable to them if the horse had been recently groomed. It subsequently became necessary to give this young man a prophylactic injection of 2 c.c. of antitoxin (horse-serum). Five minutes after the injection he was seized with an attack of difficult breathing, and within ten minutes had developed a severe asthma. With this there was falling temperature and great prostration. In short, he had a classic anaphylactic reaction. In one hour he was much better, and in two hours he had entirely recovered. The sequel was highly interesting, as during the three months following he was immune to horse emanations, as was repeatedly proved experimentally. The cure, however, was not permanent.

Wiley cites a case in which there was this same hypersusceptibility to horse emanations, in which a dose of 2 c.c. of antitoxin (horse-serum) resulted in prompt death.

Asthmatic attacks in every way analogous to those just cited are not uncommon in children, and are not infrequently confounded at first with pneumonia. The children who are subject to these attacks have them, as a rule, at frequent intervals, sometimes as often as once or twice a month. The Germans, following Finkelstein's classification, consider laryngeal spasm, tetany and eclampsia as part of the "spasmophile diathesis," and, more recently, one of us (Pisek) suggested in a monograph that all those conditions which were marked by spasm of some portion of the respiratory tract—as asthma, for example—be included in this classification. It is, of course, to be understood that this group does not include, at least specifically, those cases in which an actual physical anomaly is present. These spasmophilic conditions have long been regarded as the result,

directly or indirectly, of exaggerated irritability on the part of the child's nervous system. They are most often found in children who have suffered from disturbed chronic metabolic processes during the period of growth and development.

One of us (Pisek) recently had under observation an infant suffering from tetany in which the attack could be brought on almost at will by feeding the infant with whole milk. This child presented evidences of rickets and symptoms of intestinal indigestion. Later it did very well on a whey-cream mixture, but it was three months before untreated milk could be added to its dietary without causing marked symptoms of tetany to appear. Perhaps symptoms which we have long considered as due to unstable nervous equilibrium are in reality mild forms of anaphylactic reaction. The suddenness of onset and rapidity with which they disappear would certainly suggest it. It is certain that they occur under circumstances which most favor absorption of unchanged or slightly changed proteins from the intestinal tract, for we have already shown that an irritated gastro-intestinal tract is most favorable for absorption of antigen in sensitized guinea-pigs. Under these circumstances death would not ordinarily occur for the reason that the antigen would be absorbed only in minute quantities, which of itself would tend either to do away entirely with the attack or, if the amount were slightly larger, to produce mild symptoms.

In this connection it is not unreasonable to suggest that some of the severer types of convulsive seizures may be anaphylactic in origin. It is recognized that previously healthy children attacked with acute infectious gastro-enteritis rarely have convulsions at the outset. A study of our clinical cases is evidence that children who have suffered from a mild and insignificant digestive disturbance for some time are most apt to be seized with a convulsion when the intestinal disturbance becomes exacerbated.

Rist, Axamit, Rosenau and Anderson, Kraus, Doerr and Freiberger have all shown that bacterial proteins are capable of causing the anaphylactic reaction in guinea-pigs. Freiberger and Goldschmid found that by leaving the bacteria in contact with the amboceptor (specific), then later carefully washing and finally mixing them with fresh guinea-pig serum, after a while a poison was produced which in doses of 2 to 4 c.c. quickly caused the death of guinea-pigs with all the symptoms of anaphylaxis. It would seem from these findings, paradoxical as they appear, that these reactions are merely quantitative differences in the same curative processes. We must, therefore, regard both of these factors in our consideration of infectious diseases. With the invasion of bacteria the formation of antibodies begins, and as these antibodies are formed there is an anaphylactic reaction taking place. The formation of the resulting poison or anaphylactin is at first so small in quantity as not to cause immediate

death. At this point another interesting factor enters. Vaughan has shown that anaphylactic reactions may be prevented in whole or in part in a sensitive guinea-pig by preceding the second dose with a very small quantity of the antigen. As the production of anaphylactin in the earlier stages of an infection is very minute, the constant tendency is to diminish the severity of the anaphylactic reaction. As an example let us consider a sickness with a crisis, as pneumonia. If, on the one hand, the production of antibodies takes place rapidly enough to destroy all the bacteria, and, on the other hand, the number of bacteria are insufficient to form a toxic dose, then there follows a critical healing. On the contrary, if the amount of strange protein is so great as to cause the formation of a toxic dose, exitus follows. Again, if the amount of antibody formed is small, then the destruction of bacteria will be so minute as to cause a mild grade of anaphylactic reaction, and then we will have the clinical picture of a protracted course. The temperature-curve in a pneumonic crisis is quite typical, often falling to or below normal in a comparatively short space of time. *This is in accord with anaphylactic phenomena.*

The conditions as described in pneumonia hold good in these exanthemata, in which there is an incubation period of seven to ten days, the organism being flooded with parasite albumin, and the final critical formation of anaphylactoxins, with the appearance of the antibodies. The course of the exanthemata runs a close parallel to the serum disease, and the analogy between these diseases and vaccination for small-pox is certainly close, as von Pirquet pointedly put in his work on "Serum Krankheit."

Special reference may also be made here to the nephritis which follows scarlet fever. It is quite apt to appear at about the third week of the illness, and may be looked on as a sort of relapse. The explanation lies in the probability that the formation of antibody was not sufficient to destroy all the bacteria, and with their growth in numbers a sufficient amount of anaphylactoxin is produced to cause a relapse which is local and not general in character. This assumption is borne out by the observations of Shick, who noticed that during the third week other symptoms, such as lymphadenitis, characteristic rise of temperature, and occasional relapse all occurred at about this time and only at this time. This very process occurs in tuberculosis and typhoid. Thus it is seen that we have, on the one side, the bacterial albumin, and on the other the formation of antibodies and the partial destruction of the bacteria, with a more or less active anti-anaphylaxis, in this way accounting for relapses or a protracted course.

It has been our effort to correlate some of the many isolated facts which have come from the laboratory, and to attempt to bring them into intimate relation with clinical pediatrics. Through such experiments a clearer conception of the fundamental problem of disease has been

obtained, and should lead to improved methods of prophylactic and curative treatment. In the theories advanced, perhaps, will be found the explanation of some of our empirical treatment, and it is hoped that this contribution will suggest new lines of treatment and stimulate other clinical workers to gather evidence in this branch of medical science.

36 East Sixty-Second Street.

THE FUNDAMENTAL REQUIREMENTS OF AN INFANT'S NUTRITION *

JOHN HOWLAND, M.D.
ST. LOUIS

The requirements for an adult's nutrition under the most varying circumstances are definitely known. The amount of food that is necessary to keep him in a state of equilibrium when at rest, when exercising moderately and when undergoing the most violent exertions, has been determined with scientific accuracy. These determinations may be repeated as often as wished, and, provided they are properly made, will give uniform results. They are laborious and time-consuming, but yield trustworthy data because, with the assent and the cooperation of the adult subject, the conditions can be absolutely controlled.

It is not so with children or infants. There is no reason to believe that in them the laws of nutrition differ in any marked way from those of the adult, but the control of conditions so as to make our results trustworthy is extremely difficult, and we are able to obtain, at best, only a part of the information that we wish, accurate though this be. I shall speak of this more fully later, because it is the one, and apparently the only, insurmountable obstacle in the way of the most scientific and satisfactory accuracy in determining the food requirements of the infant.

There are certain fundamental facts that must be considered in dealing with this subject. The warm blooded animal requires energy for the life processes of the organism, the heart-beat and circulation, the respiration and the activity of the various organs and glands, and the heat produced by these processes, with the assistance of the physical vasomotor control, maintains the cells at their normal tropical temperature, in which they functionate to the best advantage. Energy is also required in addition for the animal's endless muscular activities. The energy that the body expends is all given off and may be measured as heat—all except that energy contained in substances in the urine and feces that have failed of complete combustion and which for the present may be disregarded. It is therefore quite logical to speak of the energy expended in terms of heat-units and of the food that is ingested to furnish this energy and which is readily converted into it, in the same terms.

If the output is known, the human body may be retained in a state of equilibrium by furnishing an amount of energy in the form of food

*Read at the meeting of the American Pediatric Society, Lake Mohonk, N. Y., June, 1911.

equal to this, and, as I have said, the output is, especially in adults, capable of being measured. It is obviously impossible to do this for each patient that must be fed, but Rubner's work makes this no longer necessary. Pettenkofer and Voit measured the output of different men under the same conditions, but were unable to decide what it was that determined the varying amount of energy loss. It was Rubner's great service to point out that the heat production and dissipation, or, in other words, the amount of energy lost, are, under similar circumstances, proportional to the surface area of the body. This law enjoys the widest applicability. The lion and the mouse, the infant, the grown man and the giant give off the same amount of heat per square meter of body surface, provided the conditions are the same. The importance of the skin surface is thus apparent.

An accurate method for the determination of the body's surface area is, therefore, necessary. The formula usually employed is

$$\sqrt[3]{\text{Wt. in gm.}^2}$$

multiplied by a constant, 12.3 or 11.9. For the average well-nourished child or adult, this formula gives excellent results. It is not, I believe, from the results of some of our experiments, accurate for poorly nourished or emaciated beings, and a formula which will give information as to the surface area of these is desirable and capable of being constructed.

We are further indebted to Rubner for determining by a series of thorough and painstaking experiments the utilization of the various foodstuffs and the amount of energy that each is capable of furnishing to the body under normal conditions of digestion, assimilation and excretion. Fat furnishes to the body 9.3 calories of energy per gram ingested, sugar 4.1 and protein 4.1, without reference to the products of incomplete combustion that are eliminated in the urine and feces. The saving of labor as a result of these determinations has been immeasurable, and it is because of these determinations that we may disregard the elimination of the products of incomplete combustion in the urine and feces.

In order to determine the food requirements of an infant, we begin with the assumption that the energy required to keep him in a state of equilibrium is equal to his output. If then, we measure accurately his output, we know definitely the amount of energy required to keep him in equilibrium. To this must be added the amount of energy necessary for his growth. But in order to measure the output, the conditions must be always the same and with the child the conditions can be the same only during sleep. Nothing alters the metabolism so much as mechanical work, and when awake the infant is always performing this, and the amount that each one performs is by no means the same and cannot well

be estimated, though in the individual case it may be experimentally measured.

Rubner and Heubner dispose of the necessity for keeping the conditions always the same by saying that an infant cannot perform a very measurable amount of work, and that whether he is awake or asleep will not greatly alter the results. Their determinations were always made over prolonged periods, twenty hours out of the twenty-four, with the child sometimes awake, active and crying, and sometimes asleep. Schlossmann's results were obtained in much the same way.

During the last year in Dr. Lusk's laboratory, we made experiments with different children with a calorimeter of the Atwater-Rosa-Benedict type, especially constructed for use with small children and animals, which allows a determination of the heat produced, as well as of the oxygen consumed and the CO_2 excreted, with an error of less than 1 per cent. We could show, first, that it is possible to use for comparison only sleeping hours, and that the increase in metabolism in the waking hours is very great over that in the sleeping. For instance, one boy, J. E. N., who produced during sleep 961 calories per square meter of body surface, calculated for twenty-four hours, produced 1,065 calories, similarly calculated, when awake, and 1,130 calories when crying; and another, W. McG., 1,092 calories when asleep, 1,264 when awake, and 1,514 when vigorously crying.[1] Schlossmann has also shown by determinations of the respiratory exchange on the same infant when asleep and when crying, that the metabolism could be nearly doubled, and that an infant weighing only 5 kilograms, when vigorously crying, expended one-fifth as much energy as a full-grown man at hard labor.

It is obvious, then, that children can be investigated satisfactorily only during sleep. This is unfortunate. It makes the one weak link in the whole chain. We can measure exactly how much energy is given off, and consequently how much is required, during the absolutely quiet hours, but the extra amount necessary for muscular exertion remains undetermined.

We made many experiments on a healthy well-nourished child 3 months of age, weighing 4.75 kilos, or a little over 10 pounds. He was fed every four hours during the twenty-four, so as to keep his metabolism as uniform as possible. He was put in the calorimeter shortly after a feeding, and his metabolism determined during a period of three hours, but only sleeping hours were used for the averages. It was found that he produced heat which, calculated in the ordinary way per square meter

1. The difference in the calculated metabolism of these two children when sleeping I believe to be due to the fact that the formula employed for calculating the surface area does not give correct results with poorly nourished children. The second child though lighter than the first was 3.5 cm. longer. Too small a calculated surface area gives too high a metabolism per square meter of surface.

of body surface for twenty-four hours, was equal to 952 calories.[2] I think it would be safe to say that the requirements for an infant completely quiet would be not very far from this, and that from 940 to 975 calories per square meter a day would allow sufficient latitude.

There are no figures with which these may be compared, as the heat produced by children has never before been directly measured; nor have the sleeping usually been separated from the waking hours, as it had not seemed sufficiently important to do so. Rubner's and Heubner's determinations were made, as I have said, over twenty hours in the twenty-four, the children being awake part of the time. It was impossible to continue the experiments throughout the whole twenty-four hours on account of the feeding, and as the most active periods were those shortly before and after feeding and during the bath, much of the effect of the activity was lost. It cannot, therefore, be considered that their twenty hours represent accurately an average of the twenty-four.

Their determinations on different children were 1,054, 973, 1,106 and 1,180 calories per square meter per twenty-four hours.[3] The increase over the figures which we obtained is undoubtedly to be accounted for by the mechanical work that their children performed while awake. The highest figures that they ever obtained, 1,180, were with a very active child who cried much of the time.

If we consider that 940 to 975 calories per square meter of body surface in twenty-four hours is the requisite in sleep, we can only estimate the extra amount required by muscular exertion, and this estimation is extremely difficult, and any errors likely to be enormous. One child differs so much from another in all of his habits; the first may sleep twenty hours out of the twenty-four and be peaceful, quiet and lethargic, seldom crying, and lying contentedly still; the second may sleep only fourteen or fifteen hours, and when awake may be constantly in motion, crying, struggling, turning and twisting, and in all of these extra hours he demands more energy which, as may be seen from the figures that I have quoted, may exceed the energy-demand in the sleeping hours by 40 per cent. or more.

I have reiterated this in order to emphasize just where the difficulty lies. We know the resting requirements, and we know sufficiently accurately the requirements of growth. Cammerer, by the statistical method, which determines the total food intake and urinary and fecal output, showed that one breast-fed infant retained 15 per cent. of the energy-content of his food for growth, and another, 9 per cent. Rubner and Heubner determined that an artificially-fed child retained 12 per cent. for growth. There is apparently a fixed and definite tendency toward

2. I have used 12.3 as the factor in determining the surface area.

3. Rubner and Heubner used 11.9 as the factor in determining the surface area. I have recalculated their figures, using 12.3.

uniform growth, and a definite proportion of food is retained for this purpose. Growth is the natural tendency of the child, and energy sufficient for this must be supplied in order to keep him in a normal condition. It appears that 10 to 15 per cent. in excess of the energy required for equilibrium maintenance makes ample provision for growth.

The requirements for growth are thus seen to be relatively small and by no means explain the great difference in the nutritional demands between the infant and the adult, although before the days of exact measurements this was supposed to be the only reason why the young infant required 100 calories, and the adult 35, per kilogram of body weight. Rubner gave the true explanation, that the difference was due to the relatively greater surface area. The smaller the body, the greater the surface area in comparison with another body of similar composition. As the smaller body increases in size, its surface area becomes relatively less and less, and it is for this reason that the requirements of normal children shrink from approximately 100 calories per kilo in the first few weeks of life, to about 70 per kilo at the end of the first year, and not because the rapidity of growth has undergone any great diminution.

There are known, then, the resting requirements of the infant and the extra quantity necessary for growth, but that amount over and above the other that is necessary to compensate for the activities of the waking hours, is as yet to be obtained only by estimation.

I have refrained from approaching my topic from the side of practical application because, at the present time, it does not seem that we are in a position to utilize the results of the determinations that I have spoken of in an entirely satisfactory way. There are still some additional data that must be supplied, but that it will be possible to do this at some future time I feel reasonably sure.

But the requirements of an infant's nutrition refer to quality as well as quantity. Water must be furnished to the infant in large amount compared with the adult, on account of the infant's great cellular activity. His smaller mass of cells is called on to do almost three times the work that those of the adult have to perform, and they do this to the best advantage only when water is freely provided them.

The salts of potash, sodium, magnesium and calcium are all vitally necessary for the life processes. They are all present in the proper proportion in woman's milk, and are sufficiently represented in any dilution of cow's milk that would be used for any considerable length of time. In the majority of instances, they are in excess in the dilutions given to children, but this excess is not a factor of importance with the healthy child, which is the one that is under consideration. The salts of iron are, however, deficient both in human and, especially, in cow's milk. The large supply of iron present in the liver and other organs of the newly-born, may gradually be drawn on, and evidently is intended to be drawn

on, during the first year, but this deficiency of iron is one important reason why an exclusively milk diet should not be persisted in too long.

The fats and the sugars are the great providers of energy, and together they furnish approximately 90 per cent. of the body's requirements. To a large extent they may be used interchangeably, and an excess of one may for a time compensate for the deficiency of the other, though not indefinitely. Whatever disturbances these produce, are chiefly recognized by gastro-intestinal symptoms such as vomiting, diarrhea, or soapy stools, and so forth. A deleterious effect of either of these on metabolism, so far as the exchange of energy is concerned, has not been demonstrated.

With the protein it is different. This must be furnished in a digestible and assimilable form to repair the loss by wear and tear and to provide for growth, but beyond a certain point there is a marked disadvantage in giving protein. This is not because the casein of milk is difficult of digestion, but because of the effect on metabolism known as the specific dynamic action of protein. By this action, the total heat production of the person ingesting the protein is raised, often to a marked degree. This increased heat must be disposed of. It may be available for warming the body in cold weather, but is an added source of discomfort and possible danger in hot weather, when it is difficult to get rid of sufficient heat by radiation; and it may cause a dangerous elevation of the infant's temperature when the heat-regulating mechanism is not fully developed. In addition, the extra ingestion of protein throws additional work on the organs of digestion, and the processes of intermediary metabolism.

Two experiments that I have made indicate this very well. One child, who produced an average of 952 calories per square meter in twenty-four hours, was given, in addition to his regular diet, 15 gm. of nutrose during the twenty-four hours. Nutrose contains nearly 90 per cent. of protein. As a result of this extra protein his heat production rose to an average of 1,051 calories per square meter, or a little over 10 per cent. The metabolism of another child rose from 1,097 to 1,383, or an increase of 26 per cent., with the addition of 30 gm. of nutrose. This represents an undue, unnecessary and, at times, undoubtedly harmful tax on the organism.

It is probable that slightly less protein is required for maintenance and growth in breast-feeding than in cow's milk feeding, owing to the better utilization that can be made of the homologous protein, but the excess required with cow's milk feeding is undoubtedly slight. When feeding a normal child, protein should furnish not less than 8 per cent. and not much more than 10 per cent. of the total energy in the food. When it furnishes 15 per cent., the specific dynamic action becomes noticeable, and when it furnishes 20 per cent., the effect is very marked.

It will be seen, therefore, that in addition to the quantity of the food provided, a proper disposition of the energy among the various constituents is always seriously to be kept in mind.

PROGRESS IN PEDIATRICS

NOTICE

Circular issued by the American Orthopedic Association and the American Pediatric Society in reference to acute epidemic poliomyelitis, addressed to health authorities and boards of health.

Anterior poliomyelitis is, so far as known, a communicable disease, being communicated from one patient to another and also by means of a third person. It occurs in epidemics and tends to spread along the lines of greatest travel. There is reason to believe that it is prevented from spreading by quarantine, and with the very great prevalence of the disease in the summer of 1910 it is the opinion of this committee that it is essential that it should be made a reportable disease in all states in order that its presence may be detected and its spread guarded against.

Of particular significance are the so-called abortive cases, in which indefinite ailments occur in children in communities where frank paralysis also exists. These abortive cases of infantile paralysis are undoubtedly a source of infection, and their record and study is of much importance. In a community where cases of infantile paralysis occur, cases of illness with sudden onset of fever and meningeal symptoms should be closely watched and regarded as possibly infectious. In such cases even recovery without paralysis does not establish the fact that the case was not abortive infantile paralysis.

All cases of infantile paralysis should be strictly quarantined, sputum, urine and feces being disinfected, and the same rigid precautions should be adopted as in scarlet fever. This quarantine should, in the opinion of the committee, last for four weeks, in the absence of definite knowledge as to when the infection ends. Children from infected families should not be allowed to go to school until the quarantine is abandoned. The transportation or transfer of acute cases in public conveyances should be strictly forbidden. It would be very desirable to adopt provisional quarantine measures in suspicious cases in a community in which an epidemic prevails.

The report of all cases of infantile paralysis to the public health authorities should be enforced by law, and all deaths from this cause should be properly described and registered. A careful study of epidemics by public health authorities is strongly advised.

Robert W. Lovett, M.D., Chairman.
Henry Koplik, M.D.
H. Winnett Orr, M.D.
Irving M. Snow, M.D., Secretary.

ANATOMY, PHYSIOLOGY AND HYGIENE

School Inspection in Small Towns

(*Arthur Tracy Cabot: Boston Med. and Surg. Jour., 1911, clxiv, 633*)

Cabot advances the proposition that the best school inspection and supervision in towns and small communities is obtainable by a nurse alone. He cites the experience of two years in Canton where the method has been tried with perfect satisfaction. Inspection by a competent physician is expensive and is very difficult to obtain, because in small places the physician's close supervision

of the children is interfered with by the professional jealousy of the other physicians. The nurse in Canton looks after 900 children. She examines them at the beginning of the year and records the results in a card catalogue. She keeps a record of any illnesses they may have during the year. Children showing any infirmity of eye, ears, throat or general condition are referred to their physicians and followed up to see that they get advice and follow it. The nurse also gives talks on matters of hygiene. This teaching is reenforced by visits to the homes. Arrangements have been made with the dentists of the town to treat the poor children on certain afternoons at half price. The contagious disease problem is easily handled by the nurse working in conjunction with the board of health. The nurse has also had time to follow up the known cases of tuberculosis. The town people have been eager to cooperate in this work and to appropriate money for its support. RICHARD M. SMITH.

BACTERIOLOGY AND PATHOLOGY

Newer Investigations on the Thymus Gland and Their Importance for Pediatrics

(Heinrich Klose: Arch. f. Kinderh., 1911, lv, Nos. 1 and 2, p. 1)

The article is divided into two parts: 1. A review of the literature and of our present knowledge on the subject of the thymus gland. 2. An account of the author's experiments on the subject of the function of the thymus.

1. The author reviews the literature and the two theories as to the cause of the symptoms associated with an enlarged thymus; i. e., (1) that such symptoms are due to a pressure of the thymus on the trachea; (2) that an enlarged thymus is merely one part of the general condition of lymphatism, with which is associated a weak heart, and that to the latter are due the symptoms of asphyxia and collapse.

2. Klose then reviews the reports of twenty-three patients operated on by different surgeons. Of these nineteen recovered entirely, three died, one was improved. He considers that operation is indicated whenever the diagnosis of an enlarged thymus with pressure symptoms can be made.

The symptoms of an enlarged thymus may be classified as follows:

Subjective: (a) Symptoms of tracheal obstruction. These may begin as a stridor in respiration and develop later into a condition marked by sudden attacks of asphyxia brought on by any shock, physical or mental. Any of these attacks may prove fatal; sometimes the child dies in the first attack; (b) difficulty in swallowing from pressure on the œsophagus; (c) symptoms of compression of the large vessels of the neck by the thymus.

Objective: On inspection there is a bulging in the jugular fossa on expiration. On percussion there is dulness in a triangular space, the base of which is the space between the sternoclavicular articulations, the apex at the second rib. The *x*-ray often decides the diagnosis, but a reliable picture is difficult to take in these children. The diagnosis must often be made in the absence of physical signs on symptoms of chronic tracheal obstruction with sudden attacks of asphyxia.

Treatment: Nonoperative measures are not recommended by Klose. Radiography he considers very dangerous, as its use may lead to a complete degeneration of the organ. Tracheotomy or intubation are not effective as the obstruction lies too deep.

Operations recommended are: 1. Intracapsular shelling out of the gland and ectopexy. This is done without removing any of the sternum; it is simple and is usually sufficient to cure the condition. If it is not sufficient, 2. Left sided enucleation or excision is recommended. 3. Finally, if necessary, thymectomy after removal of part of the manubrium sterni.

EXPERIMENTAL INVESTIGATIONS ON THE FUNCTION OF THE THYMUS

1. Review of other experiments.

Basch's experiments, principally directed toward the study of the relation between ossification and the thymus, the author reviews at length. Basch operated on twenty dogs, between 3 and 4 weeks old, removing the thymus as completely as possible. In thymectomized animals, as compared to normal control animals, he found, 1. The bones remained longer in the cartilaginous state and were more pliable. 2. A greater excretion of calcium from the kidneys. 3. A greater irritability of peripheral nerves. Convulsions were quite frequent in these dogs.

Klose criticises these experiments on the ground that the thymectomy should have been performed at the height of thymus development. This, in the dog, is at about the tenth to the twentieth day of life. After this time it undergoes rapid involution until the second and third month. A thymectomy performed during the stage of involution would give misleading results.

2. The Author's Experiments.

His own experiments were carried out on fifty-four animals. About the tenth day the thymus was removed as completely as possible. The symptoms appearing in the thymectomized animals he divided into stages as follows:

1. Latent period without symptoms lasting a variable time.

2. Stage of adiposity, lasting two to three months. The dogs increase in weight as rapidly as the normal animals, becoming very fat, though the fat is spongy and pasty. He compares the condition to that summed up by the term "exudative diathesis" in children. The appetite of the animals is enormous, and the tastes abnormal.

3. Cachexia thymopriva, lasting three to six months, sometimes as long as fourteen months. The dogs now lose in weight and become very weak, especially in regard to the bones. Spontaneous fractures are common. These dogs are completely idiotic and eat anything.

4. Coma thymicum. The animals finally become comatose and die.

The bone changes he describes in detail, showing, as he says, the characteristics of rachitis, osteomalacia and osteoporosis. In growing bones the changes are those of lessened growth, with abnormal softness and pliability, resembling rachitis; in adult bones the changes are those of an increased katabolism; that is, osteomalacia and osteoporosis. Cyst-formation is present in the spongy tissue of the bones. The epiphyseal cartilage is thickened. Microscopically, together with the osteoporosis, is seen an overgrowth of cartilaginous tissue and a lessening of calcium formation.

Chemically examined the bones are found to contain only 32 to 34 per cent. of calcium, while normal bones contain 65 per cent. The relation between the calcium carbonate and the calcium phosphate is the same in the thymectomized as in the normal animals.

The author then inquires into the relationship between the thymus gland and the development of bones. He proposes the theory that the bone changes after thymectomy are due to an "oxypathy" or intoxication with an acid, which he thinks is probably nucleinic acid. He concludes that the thymus is an organ which either hinders the formation of acid in the organism or neutralizes or masks a surplus of acid.

Neurologically, Klose found in the thymectomized animals a hyperirritability of the peripheral nerves. In those animals the injection of a large amount of calcium decreased this irritability. Intravenous injection of thymus extract caused in normal animals an increased irritability, soon returning to the normal. In thymectomized animals such an injection caused no increased excitability but an increase in all the pathologic symptoms. The brains of the experimental animals he found to be swollen and edematous. The spleen is the most important compensatory organ for the thymus; in the experimental animals it shows great richness in follicles and cell divisions. Dogs in whom the thymus is removed in its involution stages show only slight changes; if, however, the spleen is removed, the dog dies.

G. L. MEIGS.

METABOLISM AND NUTRITION

Influence of Sugar on the Intestinal Flora of Children

(E. Hartje: Jahrb. f. Kinderh., xxiii, No. 5, p. 557)

Sugar plays an important rôle in the formation of acids through bacterial activity, and therefore also in the change in reaction of the bowel contents, at least, in that part of the bowel in which the change from alkalinity to acidity takes place; therefore, it is well to know the amount of sugar in the bowel contents. Hartje examined the feces for sugar, the Haines test proving the most reliable, and found it present in the feces of all normal breast-fed children. Sugar was found present in most cases when the Trommer, Nylander and Ozason tests were used; therefore he concludes that sugar is always present in the feces of normal breast-fed children, although the amount may be small, in fact, at times only a trace. The large bowel always contained sugar, and the further from the cecum the contents were tested, the greater was the amount of sugar found. Sugar was never found in the feces of children fed on cows' milk unchanged, but when this was diluted, not less than 6 to 7 per cent. of sugar being added, sugar was always found in the feces, the amount depending on the quantity ingested. When milk-sugar was added, or malt-sugar in the form of malt extract (powdered), the reaction was far more apparent than when grape- or beet-sugar was added. It is assumed that the reason for this is that the milk-sugar and malt extract were excreted in larger quantities than the grape- and beet-sugar.

A quantitative examination was made in the case of two children, one aged 1 year and 3 months and the other 1 year and 5 months. The first child suffered from acquired chronic internal hydrocephalus and the second was severely rachitic. Neither child suffered from any notable digestive disturbances. Both children were fed with a cream, milk and water mixture, to which 7 per cent. of sugar was added. The composition of the mixture corresponded to that of mother's milk. One liter contained 200 gm. cream (with 15 per cent. fat), 100 gm. cows' milk, 700 gm. water and 56 gm. sugar. Beet-sugar, milk-sugar and malt-extract, in powdered form, were used. The observation extended over a period of six days. The feces of the last three days were collected, dried over the water bath, and the sugar-content estimated according to the method of Volhard-Pflüger. The first child ingested 1,200 gm. of the mixture daily; the second 1 liter. Sugar was never found present in the urine. The results of the examination of the analyses were as follows: when a 7 per cent. solution of sugar is given, sugar is found in the feces in sufficient amount to make a quantitative estimation. When like amounts of various kinds of sugars are given, it is found that the least sugar is excreted following the ingestion of beet-sugar, a larger amount when milk-sugar is given, and the greatest amount when malt-extract is given. In the case of each of these sugars, sugar is found in the feces in relative as well as absolute quantities, the least amount being found in the case of beet-sugar, a larger amount in the case of milk-sugar, and the largest quantity in the case of the malt-extract. Relatively, that is, in a definite amount of dried feces, there is ten times more sugar when malt-extract is given than when beet-sugar is given, and from five to seven times more when milk-sugar is given than when beet-sugar is given. The weight of the dried feces varies according to the kind of sugar administered. It is greatest when malt extract is given and lowest when milk-sugar is given. The author suggests that differences in resorption may account for these findings, or the action of the sugar on the intestinal mucosa may have something to do with it. The character of the stool varies with the kind of sugar given. Beet-sugar seems to cause a dry stool of alkaline reaction, whereas in the case of milk-sugar and malt-extract the stool is mushy and neutral or acid in reaction. The author concludes that in rickets the resorption of sugar is lowered considerably and that, therefore, it appears in greater amounts in the feces than under normal conditions. A microscopic examination of the feces in the case of these two children showed that Gram-

positive bacteria were present in increased numbers and in the plate cultures the acidophil bacteria loomed up conspicuously. Sugar, then, apparently favors the growth of the acidophil organisms, provided that the sugar exceeds the albumin six to seven times. An increase in the albumin-content influences the intestinal flora to the extent of diminishing the number of acidophil organisms. The growth of these organisms is more especially favored when milk sugar or malt extract is administered. Beet-sugar and grape sugar apparently have a less favorable action on the growth of these organisms, although there is still an increase in their number. In the case of milk-sugar and malt extract, almost a pure culture of acidophil bacteria is obtained. When beet-sugar and grape-sugar are given the Gram-positive bacteria are present in greatest amount and bacteria other than the acidophils are found, so that the bacteriologic factor varies according to the kind of sugar given. The author does not confirm Sittler's findings in every particular. For instance, Sittler found that when he gave cane-sugar there was a rapid falling off in the number of *B. bifidus*, with a correspondingly rapid increase in the number of *B. birefringens*. The stool also became soapy and white in color. The author ascribes these occurrences, not to the kind of sugar given, but to the lessened amount of sugar to be found in the bowel. Bahrdt and Beifeld claim that milk-sugar influences the bifidus flora and that it is not only the absolute amount of sugar but the relative amount which is a determining factor, inasmuch as the casein is antagonistic. The author concludes that milk-sugar and malt-extract favor the growth of the acidophil organisms; they also soften the stool, make it more sour and lower the normal processes in the bowel to such an extent that little or no indican is found in the urine. In order to secure the characteristic bowel-content and the feces of the breast-milk-fed child, milk-sugar, and especially malt-extract, should be given.

ACUTE INFECTIOUS DISEASES

Meningitis in Infancy

(*John Lovett Morse: Boston Med. and Surg. Jour., 1911, clxiv, 701*)

When cerebrospinal meningitis is not epidemic at least 70 per cent. of the cases in infancy are tuberculous. A large majority of the others are meningococcal in origin. Meningitis due to other organisms is rare, and unless it develops during the course of some other disease, need not be considered in differential diagnosis. Meningitis secondary to otitis media almost never occurs in infancy. Symptoms of meningeal irritation are very common in the course of many diseases in infancy. If the fontanelle is open and not bulging the condition is almost surely not meningitis. If the fontanelle is closed a positive diagnosis can only be made by lumbar puncture. In general whenever there is any question as to the presence or absence of meningitis a lumbar puncture should be done. The symptomatology of meningitis in infancy is different from that in older children. The pulse and respiration are increased. Vomiting is common but is rarely explosive. Constipation is rare. Convulsions and manifestations of pain are unusual. Kernig's sign and knee-jerks are variable. Ankle-clonus, retraction and spasm of the abdominal muscles are usually absent. The diagnosis between tuberculous and cerebrospinal meningitis is very difficult. On the whole, the symptoms are more marked in the cerebrospinal than in the tuberculous form. It is the exception to find evidence of tuberculosis elsewhere in the body. A positive history of exposure to tuberculosis is of great value A leukocytosis is in favor of the cerebrospinal form but does not exclude the tuberculous. The tuberculin test, if positive, is strong evidence for tuberculous meningitis; a negative test is not conclusive. Lumbar puncture should be done in every case. In tuberculous meningitis the fluid runs out under increased pressure; is clear or slightly turbid; shows a fibrin clot on standing; contains

more than twenty cells to the c.mm., mostly mononuclear; shows tubercle bacilli in about 90 per cent. of the cases. In cerebrospinal meningitis the fluid is under pressure; is turbid or purulent, shows a fibrin clot or deposit of pus on standing; contains many cells—mostly polynuclear; shows the diplococcus intracellularis. In acute poliomyelo-encephalitis the spinal fluid is like that in tuberculous meningitis but contains no bacilli. Tuberculous meningitis is very irregular in onset and early symptoms. In general the early symptoms are referable to the digestive tract. The course is usually short—averaging about two and one-half weeks, and progressively downward. Extreme meningeal symptoms are unusual. It is unfair to hold out the slightest hope of recovery. Treatment is symptomatic, with repeated lumbar puncture to relieve the cerebral pressure.

Cerebrospinal meningitis shows the same types as in adults. The most common sequel is hydrocephalus. Recovery is almost certain, unless the disease is of the malignant type, if the treatment is begun within the first two or three days. Flexner's serum should be injected directly into the spinal canal and in some cases into the ventricles. Serum should be given daily, in severe cases twice daily, until all the organisms have disappeared from the fluid, and longer if the fluid is markedly purulent. Elevation of temperature or rigidity of the neck alone are indications for continuance of the injections.

Pneumococcus meningitis is one of the manifestations of a general pneumococcus infection. The spinal fluid is turbid or purulent; contains an excess of polynuclear cells; shows the pneumococcus. The course is very short and almost always ends in death.

Influenza meningitis does not cause a leukocytosis of the blood. The spinal fluid is turbid or purulent; contains many polynuclear cells; shows many organisms. The course is short; prognosis almost invariably hopeless; treatment symptomatic.

RICHARD M. SMITH.

TUBERCULOSIS AND SYPHILIS

The Beneficial Effect of Salvarsan in Syphilis of Childhood

(Johann and Zoltan von Bokay and Ludwig Vormes: Wien. klin. Wchnschr., 1911, xxiv, No. 17, p. 583)

Twenty-six patients with syphilis were treated with salvarsan. Thirteen of them were under 1 year, four between 1 and 2 years, one between 2 and 3, two between 4 and 5, two between 8 and 9 and four between 10 and 11 years of age. Only three of these children had acquired syphilis. Of the twenty-three children with hereditary syphilis, thirteen were under 1 year old; five under 2 months, four between 2 and 3 months and four over 3 months. All thirteen were well developed and well nourished, and all were breast-fed. The amount of salvarsan, given intramuscularly and subcutaneously, varied from 0.005 to 0.01 gm. for each kilogram of body weight. A second injection was given to ten children from 3 to 5 weeks after the first, whenever symptoms did not improve rapidly and the Wassermann reaction remained positive. All these patients have been watched from two to four months since being treated and results have been uniformly good. Yet these observers believe that a longer time must elapse before they can be sure of the lasting effect of salvarsan.

MAURICE OSTHEIMER.

GASTRO-INTESTINAL SYSTEM

Treatment of Intussusception in Children

(W. E. Ladd: Boston Med. and Surg. Jour., 1911, clxiv, 712)

The mortality of intussusception untreated is between 90 per cent. and 100 per cent.; treated with irrigation, inflation and enemata 70 per cent. to 80 per cent.; operated on 31 per cent. The prolonged use of irrigation or delay before

operation is responsible in part for the high mortality with laparotomy. There is still some difference of opinion about the advisability of irrigation as a preliminary or aid to operation. It seems worth trying. It should be done with the patient anesthetized. In case there is any tumor felt after injection it is safer to operate at once. Rapidity in operation is important. The patient must be kept warm. A good-sized median incision is the best. Reduction is often difficult but should be done if possible as the mortality of resection is high. Feeding should be begun as soon as possible after the operation.

RICHARD M. SMITH.

Intussusception in Children

(*James Herbert Young: Boston Med. and Surg. Jour. 1911, clxiv, 710*)

Of all causes of intestinal obstruction at all ages intussusception comprises one-third, while in infants it comprises three-fourths. Invaginations are most common at the junction of the large and small intestine; they are usually single, but may be double or even triple. The frequency of this condition in infants is due probably to anatomic peculiarities—the long mesentery, the thin intestinal wall, the greater mobility of the cecum and ascending colon. At about the fourth month, the angle between the ileum and cecum which, until this time, is a right angle, changes so that the long axes of the two become more nearly parallel. With the anatomic changes there are certain disturbances of function, most important of which is exaggerated peristalsis. Vigorous stimulation of one part of the intestine produces an annular contraction. This contraction ring is drawn into the bowel above, and the progress of the intussusception is always at the expense of the outer portion. The contraction ring remains constantly at the head of the intussusceptum. The only exception to this rule is in the ileocecal variety in which the growth of the invagination is at the expense of the inner coil of intestine. The important symptoms are pain, vomiting, bloody stools and palpable tumor (in 80 per cent. of cases). Acute diarrheas with bloody stool must be excluded. The treatment should be immediate laparotomy.

RICHARD M. SMITH.

Chronic Intestinal Indigestion

(*J. P. Crozer Griffith: Arch. Pediat., xxviii, 324*)

Griffith emphasizes that medical treatment of chronic intestinal indigestion in early life is largely of secondary importance. The overcoming of the constipation, which is such a common symptom, is important. In addition to the hygienic measures, either small daily doses of a saline laxative or of cascara, phenolphthalein or similar drug, may be required. In other cases a small amount of sulphate of magnesia or syrup of rhubarb may be added to the tonic medicines administered. In bad cases the nightly injection of olive oil or cotton-seed oil may be of service. Very often the diet may be selected to overcome the constipation, bearing in mind, however, that many of the laxative foods are more or less irritating to the bowels. As a rule, enemata are not efficient, as they operate only on the rectum. A drug is required which affects the whole of the intestinal tract. When there is much secretion of mucus from the bowel, saline douching is sometimes of service, but this practice should not be continuous, as it sometimes maintains the symptoms which it is intended to cure. The administration of a good malt extract appears to aid the digestion of starch. One should be selected known to contain a large percentage of diastase, as there is a great difference among them in this respect. In general, as far as other medicinal treatment goes, Griffith has had the best results with the combination of an alkali with a bitter tonic. For this purpose, bicarbonate of soda may be given with tincture of nux vomica, compound tincture of gentian, and an aromatic water, administered ten to twenty minutes before meals. Cod-liver oil, although theoretically an excellent remedy to improve the general health, is often con-

traindicated, expecially early in the disease, on account of its tendency to increase indigestion in many cases. The remark applies to the use of iron given for the anemia, since until convalescence is established, this may increase the digestive trouble and the constipation. The importance of resistance in the treatment is emphasized. Griffith says that unless this is maintained, and especially unless the dietetic treatment is rigorously followed for months, an improvement which has seemed very decided, and even a cure which has seemed complete, will inevitably be followed by relapse. F. C. Z.

BLOOD AND CIRCULATORY SYSTEM

Blood-Pressure in Acute Nephritis of Children

(Lennox Gordon: Arch. Pediat., xxviii, 343)

According to Gordon, the blood-pressure in children suffering from acute nephritis is raised, and this rise of pressure may be very great. In three of seven acute cases, the hypertension was very marked. This fact is of diagnostic value, as in no other disease of childhood is there to be found the same high range of blood-pressure. Those patients who had the highest pressure were those in whom only a slight trace of edema was noticeable, and also it is of interest to note that in these same patients the quantity of blood in the urine was very great, the urine, indeed, looking like pure blood; the explanation of the large quantity of blood in the urine being, probably, that a rupture of the renal capillaries had occurred consequent on the greatly increased blood-pressure. Gordon emphasizes the fact that in children it is only by means of the sphygmomanometer that changes in the blood-pressure can be ascertained with any degree of certainty. F. C. Z.

NERVOUS SYSTEM

Migraine in Children Due to Disturbances of the Function of the Thyroid Gland

(Leopold Levi and H. de Rothschild: Rev. d'Hyg. et de méd. inf., 1911, x, 2, p. 113)

Leopold Levi and H. de Rothschild again discuss the disturbances of thyroid secretion as a cause of migraine. They believe that in adults 75 per cent. of all cases of migraine are due to thyroid instability, while in children all cases are due to this cause. Ten cases in children between 9 and 15 years are reported. Under thyroid treatment these cases have either been cured, when treatment has continued a long enough time, or have been relieved while under treatment and had a return of symptoms when the treatment was omitted. Although in these cases there were seven boys and three girls they think that in children the two sexes are equally affected. In more than half the cases the condition was hereditary. The powdered gland was given in doses of 5 milligrams, 25 milligrams and 10 centigrams, usually once or twice a day. Relief of symptoms with a small dose may be followed by a return of symptoms when the dose is increased. In certain cases some symptoms were wholly or partially relieved, while others were uninfluenced by treatment. The intense, paroxysmal headache with vomiting was at times transformed into a simple headache. Urticaria, eczema and psoriasis, associated with migraine, were cured. Cases which showed evidences of both hyper- and hyposecretion were equally benefited. For permanent cure treatment must extend over a long period of time, even up to two years. J. Herbert Young.

CORRESPONDENCE

IMPORTANT CORRECTION IN DR. WALTER BREM'S PAPER ON INFLUENZAL MENINGITIS IN JUNE, 1911, ISSUE

To the Editor: In the AMERICAN JOURNAL OF DISEASES OF CHILDREN, June, 1911, I published, with Zeiler, a report of two cases of influenzal meningitis. We stated that Wollstein in her paper on the same subject (*Am. Jour. Dis. Children*, January, 1911) had failed to include one of her own cases in her summary of the literature. Dr. Wollstein in a recent conversation with me pointed out that she had included the case under the names of Agar and Avery, who had previously made a report of it, as she stated elsewhere in her paper.

I regret very much that the oversight on my part occurred, and shall be obliged if you will publish this correction.

WALTER BREM, M.D.,
Colon Hospital, Cristobal, Canal Zone.